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EFFECT OF VARIOUS AGENTS — ULTRAVIOLET LIGHT, VACCINES, TURPENTINE, NEOARSPHENAMIN AND AUTOBLOOD INJECTIONS — ON THE ENZYMES OF BLOOD AND SKIN *

A PRELIMINARY REPORT

JAY FRANK SCHAMBERG, M.D.
AND
HERMAN BROWN, B.S.
PHILADELPHIA

Within recent years, many physical agents and various nonspecific protein injections have been advocated in the treatment of cutaneous diseases and in other general morbid conditions. The roentgen rays and ultraviolet light have been employed in many skin diseases and, likewise, in tuberculosis, cancer, leukemia and other diseases. Vaccines, both specific and nonspecific, have been extensively used in many infections. Oil of turpentine has been employed to raise the resisting power of the organism in pyogenic conditions. Autoserum and autoblood injections have been successfully employed in psoriasis and in certain other dermatoses. Many other nonspecific protein injections have been credited with desirable therapeutic effects.

In view of the free employment of these various agencies, we have thought it worth while to endeavor to study the influence of some of them on that relatively little explored field, the enzymes of the body. We have largely limited our investigations to a study of the lipase and protease in the blood and in the skin.

The lipase determinations were numerically greater than the protease for the reason that, to obtain a sufficient quantity of blood for the latter, the laboratory animal had to be sacrificed. It was obviously impossible, with the method employed by us, to make comparative studies of the skin enzymes before and after treatment, as this could be determined only after the death of the animal.

EFFECT OF ULTRAVIOLET LIGHT

Ten rabbits were, at various times, exposed to ultraviolet light (Alpine lamp). The rabbits weighed about 2 kg. These were usually

* From the Research Institute of Cutaneous Medicine.

exposed at a distance of 10 inches (25.4 cm.), in such a manner as to permit irradiation of the greater part of the body. The exposure was usually twenty minutes. Many of the animals were exposed a second, third, fourth and fifth time, at intervals of a few days.

TABLE 1.—*Effect of Ultraviolet Light on Blood Serum Enzymes of Rabbits (Alpine Lamp)*

Rabbit	Treatment	Blood		Skin		
		Proteolytic Activity, Mg. Noncoagulable Nitrogen per 100 C.c.	Lipolytic Activity, C.c. Tenth Normal Sodium Hydroxid per 100 C.c.	Proteolytic Activity, Mg. Noncoagulable Nitrogen per 100 Gm. Dry	Lipolytic Activity, C.c. Tenth Normal Sodium Hydroxid per 100 Gm. Dry	Remarks
1	Before	..	37			
	3.5 hours after Alpine lamp, 10 in., 20 min.	..	30			
	17 hours after first exposure	..	29			
	4 hours after second exposure	..	23	4,200	95	Skin scaling
	48 hours after second exposure	..	24			
	4 hours after third exposure	..	22			
	72 hours after third exposure	..	30			
	4 hours after fourth exposure	..	28			
2	Before	..	99			
	4 hours after Alpine lamp, 10 in., 20 min.	..	85			
	72 hours after first exposure	..	88			
	4 hours after second exposure	..	80			
	3 weeks after second exposure	..	100	5,500	98	Skin scaling
	4 hours after third exposure	..	80			
	48 hours after third exposure	..	80			
	4 hours after fourth exposure	..	80			
	1 week after fourth exposure	..	90			
	4 hours after fifth exposure	..	72			
3	Before	..	70			
	4 hours after Alpine lamp, 10 in., 20 min.	..	62			
	3 weeks after first exposure	..	65			
	4 hours after second exposure	..	60			
	48 hours after second exposure	..	63	4,000	70	
	4 hours after third exposure	..	63			
	1 week after third exposure	..	61			
	4 hours after fourth exposure	..	55			
	24 hours after fourth exposure	..	60			
	2 hours after fifth exposure (1 hour)	..	40			
4	Before	..	49			
	4 hours after Alpine lamp, 10 in., 20 min.	..	38			
	48 hours after first exposure	..	31			
	4 hours after second exposure	..	28	3,500	50	
	1 week after second exposure	..	36			
	4 hours after third exposure	..	30			
	24 hours after third exposure	..	35			
	2 hours after fourth exposure (1 hour)	..	20			
5	Before	5	..	..	..	
	4 hours after Alpine lamp, 10 in., 20 min.	11	..	..	..	
	24 hours after first exposure	7	..	..	..	
	4 hours after second exposure	5	..	..	..	
6	Before	15	..	..	..	
	1 hour after Alpine lamp, 10 in., 20 min.	6	..	..	..	
	24 hours after first exposure	4	..	..	..	
	4 hours after second exposure	4	..	..	..	
7	Before	6	..	..	..	
	3 hours after Alpine lamp, 10 in., 20 min.	14	..	..	..	
	24 hours after first exposure	12	..	..	..	
	4 hours after second exposure	8	..	..	..	

EFFECT ON LIPOLYTIC FERMENT (LIPASE)

In Table 1, Rabbit 1 showed a titer of 37 before exposure. Seventeen hours after a twenty minute exposure, it was 29; four hours after the second exposure, 23; forty-eight hours after the second exposure, 24;

four hours after the third exposure, 22; seventy-two hours after the third exposure, 30, and four hours after the fourth exposure, 28. There was, therefore, a reduction from 37 to 28 after four exposures.

Rabbit 2 showed a reduction in lipase titer from 99 to 72 after five exposures.

Rabbit 3 after five exposures exhibited a fall from 70 to 40.

Rabbit 4 after four exposures showed a decline from 49 to 20.

Rabbit 9 (Table 2) was sensitized before exposure by an intraperitoneal injection of quinin sulphate. After three exposures, there was a slight decline in the lipase titer from 10.8 to 9.

Rabbit 10 was sensitized by the intraperitoneal injection of eosin. After three exposures, there was a decline from 5.4 to 2.2.

TABLE 2.—*Effect of Ultraviolet Light on Blood Serum Enzymes of Rabbits Previously Treated with Photosensitizers*

Rabbit	Treatment	Proteolytic Activity, Mg. Nitrogen per 100 C.c.	Lipolytic Activity, C.c. Tenth normal Sodium Hydroxid per 100 C.c.	Remarks*
8	30 mg. eosin per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 20 minutes	6	....	
	1 hour after exposure	24	....	
	24 hours after exposure	18	....	
	4 hours after second exposure	10	....	
9	10 mg. quinin sulphate per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 20 minutes	..	10.8	
	1 hour after exposure	..	8.8	
	48 hours after exposure	..	10.7	
	1 hour after second exposure	..	10.6	20 mg. of quinin sulphate per kilogram, ½ hour before exposure
	48 hours after second exposure	..	10.8	
	2 hours after third exposure	..	9	20 mg. of quinin sulphate per kilogram, ½ hour before exposure
10	10 mg. eosin per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 20 minutes	..	5.4	
	1 hour after exposure	..	4.1	
	48 hours after exposure	..	4.2	
	1 hour after second exposure	..	3	30 mg. of eosin per kilogram ½ hour before exposure
	48 hours after second exposure	..	3.4	
	1 hour after third exposure	..	2.2	30 mg. of eosin per kilogram ½ hour before exposure

* Both the eosin and quinin sulphate were injected intraperitoneally. In the control animals, neither appeared to modify the enzyme activity.

EFFECT OF ULTRAVIOLET LIGHT ON PROTEOLYTIC FERMENT (PROTEASE) IN BLOOD

Rabbit 5 (Table 1) showed a rise of from 5 to 11 four hours after the first exposure, but a decline to 5 after the second.

Rabbit 6 exhibited a decline in protease from 15 to 4 after two exposures.

Rabbit 7 showed a rise from 6 to 14 after the first exposure, and a decline to 8 after the second exposure.

Rabbit 8 (Table 2), sensitized with eosin, showed a rise from 6 to 24, and then a decline to 10.

In a general way, it may be said that ultraviolet light, in the degree that we applied it, appeared to decrease the lipase in the serum of rabbits and to increase the protease. Further, the effects of the exposures seemed temporary, the tendency being for the values to return to their original levels.

EFFECT OF ULTRAVIOLET LIGHT ON THE BLOOD ENZYMES OF HUMAN SUBJECTS

Patient 1 (Table 4), suffering from psoriasis, was exposed to the Alpine lamp (chest and back) for sixteen minutes. A marked reaction (sunburn) developed. The lipase declined from 11 to 7 and the protease from 8 to 6.

Patient 2, suffering from psoriasis, received the same exposures. The lipase declined from 11 to 8, and the protease remained unaltered. Patient 3, suffering from generalized pruritus, was exposed for twenty minutes. The lipase rose from 10.5 to 12.5, and the protease from 8 to 9.

Owing to the paucity of observations on human subjects, no definite deductions can be drawn. In two out of three of the patients, there was a decline in the lipase.

TABLE 3.—*Effect of Various Agents (Turpentine, Vaccines and Neoarsphenamin) on Blood Serum Enzymes of Rabbits*

Rabbit	Treatment	Proteolytic Activity, Mg. Non-coagulable Nitrogen per 100 C.c.	Lipolytic Activity, C.c. Tenth Normal Sodium Hydroxid per 100 C.c.
12	Before	...	20
	4 hours after intramuscular injection of 5 c.c. turpentine olive oil emulsion	...	26
13	Before	3	..
	4 hours after intramuscular injection of 5 c.c. turpentine olive oil emulsion	5	..
14	Before	...	28
	2 hours after subcutaneous injection of staphylococcic vaccine	...	35
15	Before	...	30
	4 hours after subcutaneous injection of staphylococcic vaccine	...	35
16	Before	5	..
	4 hours after subcutaneous injection of staphylococcic vaccine	7	..
17	Before	...	40
	2 hours after intravenous injection of neoarsphenamin, 50 mg. per kilogram	...	37
18	Before	4	..
	4 hours after intravenous injection of neoarsphenamin, 50 mg. per kilogram	3	..
	24 hours after injection	4	..
19	Before	...	72
	5 hours after intravenous injection of neoarsphenamin, 50 mg. per kilogram	...	51
	24 hours after injection	...	59
	72 hours after injection	...	69

EFFECT OF INJECTIONS OF TURPENTINE ON THE BLOOD ENZYMES IN RABBITS AND IN HUMAN BEINGS

The intramuscular injection of turpentine in 5 c. c. of olive oil into a rabbit was followed, in four hours, by a rise of lipolytic activity from 20 to 26. In another rabbit, the proteolytic activity rose from 3 to 5.

In a patient suffering from eczema, the intramuscular injection of 5 minims (0.3 c. c.) of rectified turpentine in 5 c. c. of olive oil was followed, in three hours, by a rise of lipolytic activity from 9 to 10, and in proteolytic activity from 8 to 10.

In a case of pemphigus, the same treatment was followed, in three hours, by a rise in lipolytic activity from 10 to 14.5, and in proteolytic activity from 6 to 8.5.

In a case of lupus erythematosus, the injection of turpentine was followed, in three hours, by a rise in lipolytic activity from 9 to 14, and in proteolytic activity from 5 to 7.

It would appear from the foregoing studies that the intramuscular injection of turpentine tends to increase the lipolytic and proteolytic power of the blood serum in both rabbits and human beings.

INFLUENCE OF VACCINES ON BLOOD ENZYMES IN RABBITS

Rabbit 14 received an injection of staphylococcic vaccine subcutaneously. Two hours later, the lipolytic activity of the blood had risen from 28 to 35.

Rabbit 15, treated in the same manner, showed a rise from 30 to 35, at the end of four hours.

Rabbit 16, treated with staphylococcic vaccine, showed, at the end of four hours, a rise in proteolytic activity from 5 to 7. As far as any deduction from these few experiments with vaccines is permitted, it can be stated that a tendency to rise in both lipolytic and proteolytic activity is suggested.

EFFECT OF INJECTIONS OF NEOARSPHENAMIN ON THE BLOOD ENZYMES OF RABBITS

Three rabbits were injected intravenously with neoarsphenamin, 50 mg. per kilogram of body weight. This, of course, is a very large dose, equivalent to three grams for a man weighing 60 kg.

In Rabbit 17, the lipolytic activity, after two hours, was reduced from 40 to 37.

Rabbit 18 received 50 mg. per kilogram of neoarsphenamin. At the end of four hours, the proteolytic power of the serum was reduced from 4 to 3. Twenty hours later, it rose again to 4.

In Rabbit 19, the lipolytic activity was reduced from 72 to 51 at the end of five hours, rising to 59 after twenty-four hours and to 69 after

TABLE 4.—*Effect of Nonspecific Agents on Blood Serum Enzymes of Human Beings*

Case	Diagnosis	Treatment	Proteolytic Activity, Mg. Noncoagulable Nitrogen per 100 C.c.	Lipolytic Activity, C.c. Tenth Normal Sodium Hydroxid per 100 C.c.	Remarks
1	Psoriasis	Before	5	8	
		4 hours after intramuscular injection of 20 c.c. autoserum	9	19	Mild reaction
		24 hours after injection	7	17	
		72 hours after injection	6	15	
		4 hours after second injection	..	21	
2	Pruritus	Before	..	8	
		4 hours after intramuscular injection of 20 c.c. autoserum	..	14	Reaction
3	Pruritus	Before	7	9	
		2.5 hours after intramuscular injection of 20 c.c. autoserum	12	11	
4	Psoriasis	Before	..	7	
		3 hours after intramuscular injection of 20 c.c. autoserum	..	12	
6	Eczema	Before	8	9	
		3 hours after intramuscular injection of 5 m. turpentine in olive oil	10	10	
7	Pemphigus	Before	6	10	
		3 hours after intramuscular injection of 5 m. turpentine in olive oil	8.5	14.5	
9	Psoriasis	Before	8	11	
		2 hours after Alpine lamp, 16 minutes exposure back and front	8	8	Marked cutaneous reaction
10	Psoriasis	Before	8	11	
		2 hours after Alpine lamp, 15 minutes exposure back and front	8	8	Marked cutaneous reaction
5	Psoriasis	Before	10	7	Temperature, 100 F.; chills
		4.5 hours after intramuscular injection of 20 c.c. autoserum	17	8	
		10 days after injection	7	8	
		6 hours after second injection serum	5	8	
13	Psoriasis	Before	12	6.5	
		3 hours after intravenous injection of 1.5 c.c. distilled water	10	6.5	
11	Acne	Before	10	8	
		2 hours after Alpine lamp exposure for 10 minutes	11	8	Treatment applied to face
12	Pruritus	Before	8	10.5	
		2 hours after Alpine lamp exposure for 20 minutes	9	12.5	Cutaneous reaction
8	Lupus erythematosis	Before	5	9	
		3 hours after intravenous injection of 5 m. turpentine in olive oil	7	14	
14	Normal	Before	15	11	
		2 hours after intravenous injection of 1.5 c.c. distilled water	8	6	
		6 days after injection	12	8	
		2.5 hours after second injection	8	6	Reaction

seventy-two hours. It would appear that, in rabbits, large doses of neoarsphenamin tend to depress the lipolytic and proteolytic activity of the blood serum.

THE EFFECT OF INTRAMUSCULAR AUTOBLOOD INJECTIONS IN HUMAN BEINGS ON THE SERUM ENZYMES

A patient with psoriasis had 20 c.c. of blood withdrawn from a vein and immediately injected into the gluteal muscles. Before the injection, the lipolytic activity of the blood serum was 8. Four hours later, it was

19; twenty-four hours after the injection, it was 17, declining to 15 after seventy-two hours. Four hours after a second injection, at the end of seventy-two hours, it rose to 21.

The proteolytic activity rose from 5 to 9 after four hours, declining to 7 at the end of twenty-four hours, and to 6 at the end of seventy-two hours.

Patient 2, with generalized pruritus, treated with autoblood in the same manner as the preceding case, showed a rise in lipolytic activity at the end of four hours from 8 to 14.

Patient 3, suffering from generalized pruritus, received an autoblood injection and at the end of two and a half hours exhibited a rise in lipolytic activity of his blood serum from 9 to 11, and in proteolytic activity from 7 to 12.

Patient 4 (psoriasis), treated with autoblood injection, showed a rise of lipolytic activity from 7 to 12 at the end of three hours.

Patient 5 (psoriasis) showed a rise in lipolytic activity from 7 to 8. The proteolytic activity rose after four and a half hours from 10 to 17; ten days later, it was 7. Six hours after a second (intravenous) injection of 13 c.c. of autoserum, it was 5.

EFFECT OF ULTRAVIOLET LIGHT ON THE LIPOLYTIC AND PROTEOLYTIC ENZYMES OF THE SKIN IN RABBITS

As the skin of treated rabbits could be tested by the method employed by us only after death of the animal, an effort was made to determine the average normal enzyme activites in untreated control animals. The skin of four untreated rabbits showed a lipolytic activity varying from 80 to 100 c. c. of tenth normal sodium hydroxid per hundred grams of dry skin, and a proteolytic activity varying from 6,000 to 8,000 mg. per hundred grams of dry skin.

Rabbit 2, after five exposures to ultraviolet light, showed a titer of 5,500 for proteolytic activity, and 98 for lipolytic activity.

Rabbit 3, after four exposures to ultraviolet light, showed a titer of 4,000 for proteolytic activity, and 70 for lipolytic activity.

Rabbit 4, after four exposures, showed a titer of 3,500 for proteolytic activity, and 50 for lipolytic activity.

The foregoing studies would seem to warrant the conclusion that exposure to ultraviolet light depresses the proteolytic and the lipolytic activity of the skin of rabbits, the former being influenced more than the latter.

Since the normal lipolytic values of the blood in our rabbits appear to be subject to wide individual variations, the same may be true of the rabbit skin. The figures submitted, therefore, in the determinations of enzyme activity in the four normal rabbit skins are given with reservation.

EFFECT OF INTRAVENOUS INJECTION OF DISTILLED WATER

A patient suffering from muscular pains was given 1.5 c.c. of distilled water intravenously.

Before the injection, the lipolytic activity was 11; two hours later, it declined to 6; six days later, it was 8. Two and a half hours after a second injection, it declined again to 6.

The proteolytic activity before the injection was 15. After two hours, it declined to 8; at the end of six days, it was 12. Two and a half hours after a second injection, it was reduced to 8.

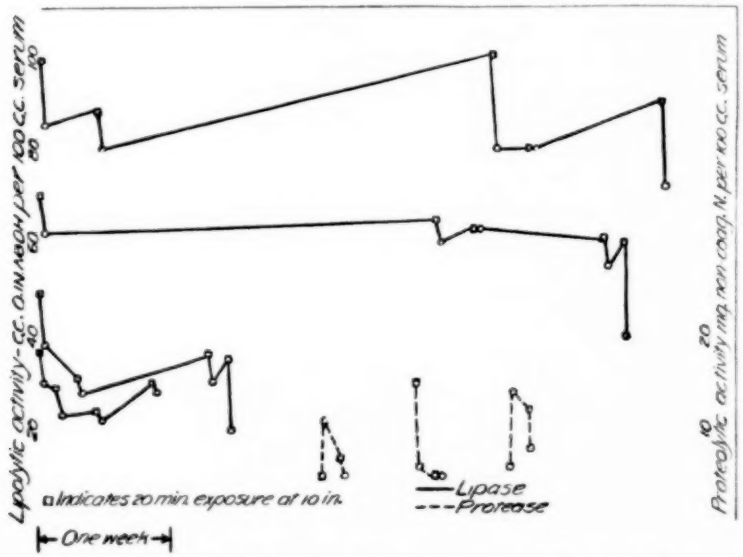

Chart 1.—Course of lipolytic and proteolytic activity of the blood serum of rabbits under influence of ultraviolet light.

Another patient suffering from psoriasis received an intravenous injection of 1.5 c.c. of distilled water. At the end of three hours, the lipolytic titer declined from 12 to 10, and the proteolytic titer remained the same, at 6.5.

METHODS

The following modifications of the methods of Jobling, Petersen and Eggstein [1] for serum protease and lipase were used:

Serum Protease.—To 1 c.c. of clear, hemoglobin-free serum in an 18 mm. diameter tube, graduated at 10 c.c., was added 2 c.c. of chloro-

1. Jobling, J. W.; Petersen, W., and Eggstein, A. A.: J. Exper. Med. **22**:129, 1915.

form. The tube was shaken sharply until a milky emulsion was formed. A control tube containing 1 c.c. of serum was heated on the water bath for thirty minutes at 60 C., after which 0.5 c.c. of toluene was added. Both tubes were stoppered with cotton and incubated for 48 hours at 37 C. From time to time, the chloroform tube was shaken to maintain the emulsion. Two cubic centimeters of water was then added to each tube, and 1 c.c. of a 20 per cent. solution of sodium chlorid in 10 per cent. acetic acid. Both tubes were then warmed to remove the chloroform and toluene and placed in boiling water for ten minutes. The tubes were then cooled, diluted to 10 c.c., filtered, and the nitrogen determined on 5 c.c. of the titrate by the usual micromethod. The difference in the nitrogen values, calculated to 100 c.c. of serum, is a measure of the proteolytic activity of the serum.

Serum Lipase.—One cubic centimeter of blood serum, 1 c.c. of neutral (phenolsulphonephthalein) ethylbutyrate, 1 c.c. of toluene and 7 c.c. of 0.85 per cent. salt solution were placed in a 100 c.c. Erlenmeyer flask. To another flask were added 1 c.c. of ethylbutyrate, 1 c.c. of toluene and 8 c.c. of 0.85 per cent. salt solution. To a third flask were added 1 c.c. of blood serum, 1 c.c. of toluene and 8 c.c. of 0.85 per cent. salt solution. Each flask was shaken 100 times, stoppered with cotton and incubated at 37 C. for four hours. The flasks were then placed in ice water, 15 c.c. of neutral alcohol and 4 drops of a 1 per cent. alcoholic solution of phenolsulphonephthalein added to each and then titrated rapidly with tenth normal sodium hydroxid. The titer, corrected for the blanks, when calculated to tenth normal per hundred cubic centimeters, was taken as a measure of the lipolytic or esterase activity.

The skin enzymes were determined according to the methods of Sexsmith and Petersen [2] except that a 1 per cent. skin suspension was used.

The proteolytic activity was determined by starting with an initial p_H of 5.5. For the autolysis, however, the initial reaction of the suspension was not altered.

A search of the literature reveals very sparse data bearing directly on the studies here reported.

Wells [3] says:

> In view of the fact that enzymes and antibodies in solution are quite readily weakened or destroyed by the action of light, it is possible that intracellular enzymes may be similarly destroyed by light, with resulting cell death.

2. Sexmith, E., and Petersen, W.: J. Exper. Med. **27**:273, 1918.
3. Wells, H. G.: Chemical Pathology, Ed. 3, Philadelphia, W. B. Saunders Company, 1918, p. 374.

Bering [4] found that chemically active light rays have a direct action on oxidizing enzymes.

Burge, Fischer and Neill [5] state that hormones, proenzymes and enzymes are destroyed by exposure to ultraviolet radiation. The rate of destruction is proportional to the amount of energy applied. (Experiments were performed in vitro, the enzyme solutions being subjected to long exposures, from one to three hours, and then tried out for activity on definite substrates.)

Jobling and Petersen [6] conclude that the serum ferments are practically unaltered by a primary injection of a foreign protein. Acute

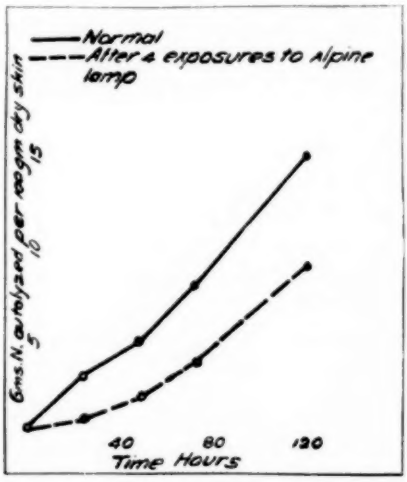

Chart 2.—Comparative autolysis of normal rabbit skin and that of rabbit exposed to ultraviolet light.

shock produces an instantaneous increase in protease, followed later by an increase in serum lipase. They state that the shock is produced by the protease splitting various proteins down to the toxic peptone stage.

Jobling, Petersen and Eggstein [7] found that the intravenous injection of killed organisms is followed by the mobilization of nonspecific protease and lipase; the rapidity and extent of this reaction depend on the toxicity of the organism and on its resistance to proteolysis. The temperature and leukocyte curve bear no relation to the ferment changes.

4. Bering: München. med. Wchnschr. **59**:2975, 1912.
5. Burge, W. E.; Fischer, W. R., and Neill, A. J.: Am. J. Physiol. **40**:425 (May) 1916.
6. Jobling and Petersen: J. Exper. Med. **22**:401, 1915.
7. Jobling, Petersen and Eggstein: J. Exper. Med. **22**:603, 1915.

Pincussen and Anagnostin [8] studied the effect of roentgen rays and nitra-lamp radiation on the serum lipase. The results, in general, showed that radiation of either the serum or the animal from which the serum was taken reduced the lipase activity. On the other hand, diathermy, as well as galvanism, when applied to the living animal, led to a significant increase.

It has been found that ferments lose their power under strong exposure to light.[9] Ferments may be destroyed by exposure to the visible as well as to the ultraviolet end of the spectrum. Green [10] found that amylase is destroyed by short wave length rays. On the other hand, the visible rays activate this enzyme through influence on the zymogen.

Chymosin, katalase and peroxidase, which are but slightly injured by exposure to the visible rays, are readily and permanently made inert by exposure to the short wave rays. The action of long wave rays on enzymes was first described by Downes and Blunt, the discoverers of the bactericidal action of light.

Bering and Meyer [11] demonstrated that peroxidase, exposed to light, acquired an increased activity. This was more particularly true of the short wave lengths.

It will be seen from the foregoing references that all these experiments were carried out in vitro.

That intracellular ferments may be influenced by light intra vitam was shown by the careful researches of Ostwald [12] on the peroxidase and katalase content of different heliotropic animals. The katalase content of living "räupchen" of porthesia chrysorrhea is strikingly lessened by exposure to light. The physiologic production of katalase is apparently favored by green light, but restricted by violet light. The production of peroxidase is stimulated to the same extent that katalase is destroyed.

Pincussen [13] believes that all cells possess their own ferments, which may be thrown into the blood when the cells break up. He states that exposure to light stimulates this.

CONCLUSIONS

1. Ultraviolet light, in the strengths used by us from an Alpine lamp, appears to decrease the lipolytic activity of the blood serum both

8. Pincussen and Anagnostin: Biochem. Ztschr. **128**:268, 1922.
9. Hausmann: Grundzüge der Licht-biologie und Pathologie, Berlin, Urban and Schwarzenburg, 1923.
10. Green, quoted by Euler: Chemie der Enzyme, München-Wiesbaden, 1920, p. 197.
11. Bering and Meyer: Strahlen-therapie, **1**:411, 1912.
12. Ostwald: Biochem. Ztschr. **10**:1, 1908.
13. Pincussen, quoted by Hausmann (Footnote 9, p. 30).

in rabbits and in human beings. On the other hand, the proteolytic activity of the blood serum appears to be increased.

2. The intramuscular injection of therapeutic doses of turpentine in olive oil tends to increase the lipolytic and the proteolytic power of the blood serum both in rabbits and in human beings.

3. Limited observations on the effect of subcutaneous injections of staphylococcic vaccines suggest that they tend to increase both the lipolytic and proteolytic activity of the blood serum.

4. The intramuscular injection of freshly drawn autoblood appears to stimulate an increase in the lipolytic and proteolytic activity of the blood serum.

5. The injection of large doses of neoarsphenamin in rabbits (equivalent to 3 gm. for a man weighing 60 kg.) tends to depress the lipolytic and proteolytic activity of the blood.

6. Observations on two cases suggest that the intravenous injection of small quantities (1.5 c.c.) of distilled water tends to decrease the lipolytic activity of the blood and perhaps the proteolytic power.

7. The exposure of rabbits to ultraviolet light from an Alpine lamp decreases the lipase and the protease in the skin of an animal.

8. In summarizing, it may be said that injections of vaccines, turpentine and autoblood appear to increase the lipase and protease in the blood, while huge doses of neoarsphenamin and small doses of distilled water tend to decrease them. Ultraviolet light depresses the lipase, and stimulates the protease.

PATHOLOGIC CHANGES OCCURRING IN WHITE RATS RAISED ON DIETS DEFICIENT IN VITAMIN A*

IRA A. MANVILLE, M.D.

PORTLAND, ORE.

It now seems well established that there are two distinct factors concerned in the Fat-Soluble A vitamin. One is antirachitic. The other is antixerophthalmic and growth promoting, and retains the appellation vitamin A.

The bony lesions following a dietary regimen in which the antirachitic factor has been lacking have been described.[1] Among other lesions resulting from this deficiency, Kauffman, Creekmur and Schultz [2] have described changes in the middle ear resulting in varying degrees of deafness. Grieves [3] also claims that dental caries is another manifestation of the upset in calcium metabolism.[4] There has also been mentioned in connection with rickets of a certain type an upset in nervous equilibrium due to an improper calcium balance,[1] while Reynolds and Macomber [5] assign to the same cause some cases of sterility.

The absence of vitamin A from an otherwise adequate diet will cause a cessation of growth soon followed by the characteristic eye lesions so well described by Mori.[6] He also showed that the salivary glands undergo a cessation of secretory activity analogous to that undergone by those of the orbit. Daniels, Armstrong and Hutton [7] have recently emphasized the fact that the lack of vitamin A is the specific

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* From the department of physiology, University of Oregon Medical School.

1. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmons, Nina: Is There More Than One Kind of Rickets? Am. J. Dis. Child. **23**:91-106 (Feb.) 1922.

2. Kauffman, A. B.; Creekmur, Francis; and Schultz, O. T.: Changes in the Temporal Bone in Experimental Rickets, J. A. M. A. **80**:681-685 (March 10) 1923.

3. Grieves, C. J.: The Effect of Defective Diets on Teeth, J. A. M. A. **79**:1567-1573 (Nov. 4) 1922.

4. We have noted in our own work a greatly increased fragility of the teeth of deficient rats, and, in some instances, we have found a stub where a brittle tooth had snapped off.

5. Reynolds, Edward; and Macomber, Donald: Defective Diet as a Cause of Sterility, J. A. M. A. **77**:169-175 (July 16) 1921.

6. Mori, S.: Changes in Para-Ocular Glands Which Follow Administration of Diets Low in Fat-Soluble A; Effect of Same Diets on Salivary Glands and Mucosa of Larynx and Trachea, Bull. Johns Hopkins Hosp. **33**:357-359 (Oct.) 1922.

7. Daniels, Amy L.; Armstrong, Margaret E., and Hutton, Mary K.: Nasal Sinusitis Produced by Diets Deficient in Fat-Soluble A Vitamin, J. A. M. A. **81**:828-829 (Sept. 8) 1923.

factor that permits another disorder to develop which they have termed paranasal and mastoid sinusitis. Because of this deficiency, bacterial invasion of the mucous membranes of the ear and nasal cavities is made possible.

The results of experiments with vitamin A deficient diets seem to justify two general statements: first, that cellular activity is minimized, and second, that out of this reduction in activity comes an increased susceptibility to infections hastening the termination of the experiment. A finer analysis of the first of the preceding statements will show that the results of a lessened cellular activity will depend on the type of cell affected. If there is a curtailment of the activity of somatic cells, the first result will be failure to produce new cells—stoppage of growth; the second, inability to replace cells already existing—loss of maintenance, and the third, actual regression. If there is a diminution in the activity of glandular cells, the results will vary with the type of gland affected and, in general, there will be a lessened resistance to infection, malnutrition and sterility.

Vitamin A is a substance necessary for the normal functioning of the body tissues. It is not clear just how it meets this necessity. It may either be one of the essential ingredients needed in cell structure or it may act as a hormone making available some necessary component in cell formation. In either case, it is absolutely essential for the cell multiplication necessary for growth and maintenance.

In general, growth is proportional to the supply of vitamin A. Normally, a rat matures at three months of age. It also obtains about three fourths of its body weight in that time. At the very time in a rat's life when the bulk of the vitamin A supply is no longer needed for growth, the reproductive organs begin to function. Most of the vitamin A intake during the first three months of a rat's life is used for the formation of new cells throughout the body. When the animal has practically attained its growth and the majority of the new somatic cells needed are those required for replacement, the vitamin A supply is utilized in new quarters, in the glandular elements, where cell increase suddenly takes a tremendous impetus, which it maintains throughout the vigorous span of a rat's life. The rat is now mature; the sexual function is established, and the nervous, respiratory and digestive systems have become stabilized by proper and sufficient glandular activity.

The purpose of this paper will be to offer observations in support of the preceding statements, and to show that a vitamin A deficiency causes such a reduction in cellular activity as to amount to a pluriglandular deficiency, and that this in turn brings about secondary changes directly leading to death.

The technic of the feeding experiments conforms as closely as possible to the rules governing such experimentation. A description of methods has appeared so many times in the literature that, aside from saying no departures were made from the best approved methods, nothing further will be added.

Our work confirms in many respects the findings mentioned above, and brings out additional pathology of this deficiency. For some time, we have observed that our rats on a vitamin A low diet, when reaching a stationary nutritive regimen, could be made to do much better by the simple expedient of moistening their food. The food is ordinarily in a semidry, caked condition. For the first seven or eight weeks, they eat enough of the food in this condition to produce fair growth curves. Then ensues a period of variable length, from one to three weeks, when they either become fussy and scatter the food about the cage or act indifferently toward it. If sufficient moisture is now added to the food, this condition does not become so acute. As implied above, we are inclined to attribute this to the xerostomia and to consider it an early sign of the specific vitamin deficiency. This dry condition of the mouth is further demonstrated in the following manner: Several small cotton swabs of uniform size and firmness are made. They are slightly moistened in a solution of brom thymol blue, which will turn blue when in contact with the alkaline saliva. One swab is used for each rat. An equal number of normal rats are similarly treated for controls. The moistened applicator is placed in the rat's mouth and thoroughly swabbed about. In the normal animals, the cotton immediately takes on a very dense blue color, while with the test animals the color appears fainter in hue and occurs in spots and patches, indicating a lessened amount of salivary secretion.

With the procedure just described, a fairly accurate estimate may be obtained of the hydrogen ion concentration of the saliva, of the secretions of the vagina and the rectum, of the peritoneal fluid and of the blood serum. In such instances, the swabs were matched for color to a series of swabs made from buffer solutions of known hydrogen ion concentration. Thus it was that we found that the reaction in the mouth of a rat suffering from xeropthalmia and xerostomia had changed from the normal alkaline condition of p_H 7.4 to an acid one of p_H 6.6. This was due to a decrease in the alkaline saliva, increased stasis of intra-oral material and bacterial activity.

This condition of dryness does not exist in the mouth alone. Mori [6] found it in the eyes. We have found that it involved the upper part at least of the trachea, for such rats, when given painful stimuli, are unable to squeal as do normal rats when similarly stimulated, but give forth, instead, a dry, husky cry or none at all, depending on the degree of

involvement. This attempt at a cry is accompanied by the usual facial grimaces, and is undoubtedly an attempt on the part of the rat to give voice to his discomfort. This dysarthria is additional evidence of the general xerosis due to glandular insufficiency, and is analogous to a similar condition, described by Mori,[8] occurring in school children suffering with xerophthalmia.

This lack of glandular activity does not seem to be limited to the para-ocular, paranasal and para-oral glands. The dryness of the feces and of swabs applied to the rectum, large bowel and vagina seems to indicate that here, too, is a lessening in the secretions. There are still other evidences of vitamin A deficiency that can very well be associated with the lack of glandular activity noted in the foregoing. These are the lack of gonadial activity as manifested by variations in reproductive ability, marked underdevelopment of the seminal vesicles, lessening of the mammary secretion, due both to incomplete development and to decreased function, and a curtailment in the secretory activity of the oil glands of the skin, resulting in a dry, bristling hair, which falls out much more readily than that of normal animals. More could be said concerning the changes occurring in the reproductive system, but this material is being reserved for a future report.

The marked decrease in cellular activity noted above should be considered the primary pathologic change resulting from vitamin A deficiency. The decrease in secretions promotes desquamative changes; destroys the action of cilia; lowers bactericidal ability, and, in many other ways, provides portals for entry of numerous organisms that soon produce pyogenic lesions with their associated complications. These should be considered as secondary pathologic changes resulting from a lack or shortage in vitamin A.

Our necropsy records of such deficient rats show that a large majority of them had pyogenic infections. In many instances, we found the posterior third of the tongue the seat of abscesses ranging in severity from a single small centrally placed abscess to an involvement in which there was almost total destruction of that portion of the tongue. The organisms causing these central abscesses seemed to have gained entrance either through the foramen cecum or that tissue representing its vestiges. Other abscesses, more laterally placed and generally much more extensive and destructive, had their origin from material escaping from the ruptured salivary ducts leading from the submaxillary and sublingual glands. In all cases of lingual abscesses, the sublingual and submaxillary glands were found infected, their ducts greatly distended with purulent material and the region of their opening beneath the tongue always marked by cystic dilatation. Other abscesses have been found on the borders of the lips. These oral abscesses must be of prime importance

as reasons for the rats' refusal to eat, and undoubtedly share in the explanation of their nutritive decline.[8]

In most cases, mucopurulent material has been found in the nasal sinuses and middle ear due to direct extension from the nasal tracts and eustachian ducts. Large purulent plugs have been found in the nasopharynx which had their origin as drainage from the higher respiratory areas. These plugs frequently acted as a serious menace to free respiration. In these particular instances, the rats would have paroxysmal spells of sneezing, which would produce marked cyanosis and pronounced exhaustion. It is likely that during these paroxysms particles became dislodged and were aspirated further into the respiratory tract, producing numerous purulent deposits in the lungs. Necropsies on such animals seemed to indicate such a course. Thus, the infection was spread to the pulmonary tissues, and extensive empyemic areas developed. We have seen numerous cases in which the lung tissue was almost entirely replaced by immense accumulations of pus. These animals did not seem to die so much from the infection itself as from the gradual obliteration of the respiratory tissue and the resultant asphyxia. Respirations would become more dyspneic, and oxygenation so poorly accomplished that the rat would have to minimize all physical effort. Even then he would gradually become more cyanosed; lose

8. I was an interested witness at a necropsy recently held at the Multnomah County Hospital. The body examined was that of a Chinese, aged 55. He was 5 feet 9 inches (175.2 cm.) in height, and weighed 100 pounds (45.4 kg.). His body was very emaciated. No clinical diagnosis had been made, as he persistently refused to answer all questions, stating over and over again that he was all right. Physical examination was negative, except for small enlargements on both sides of the throat in the region of the submaxillary glands. The teeth were extremely bad. The urine was negative, except for a trace of albumin and a few casts. The history, so far as obtained, was also negative. He was in the hospital only a few days before he died, and during that time steadily refused all food, drink and medication. Toward the last, he even refused to have his temperature taken by mouth. He talked very little, and then only by urging. The temperature averaged 97 F., running at times as low as 94 and as high as 98.2. The pulse was 80, and the respirations 20. The only complaint was a "burning in the throat." He rapidly grew weak, and toward the last was occasionally irrational. Outside the usual senile changes and evidences af arteriosclerosis, the necropsy findings were negative, except for these very significant points: A large abscess beneath the tongue was found at the point of exit of the submaxillary ducts; the ducts themselves were distended with pus and the glands were greatly enlarged and engorged with purulent material; the esophagus presented numerous submucous abscesses, and the posterior portions of the lungs were congested. Although the cause of death was given as hypostatic pneumonia, it is evident that this is only a partial truth and does not explain the primary condition leading to this result. It is difficult to understand how a human being living in the midst of our modern life could die from a deficiency such as described above, yet it must be considered a possibility. Especially is this true when one considers how near to the border of adequacy are many of the menus of an average person's diet.

steadily in body heat, and, finally, die of exhaustion and malnutrition and the associated low grade intoxication.

By direct extension from the nasopharynx, the infection spread to and involved the middle ear, and, in some cases, became so severe in this location that the vestibular apparatus also became involved, causing the animal to show circus movements. Frequently, the stomach is found containing purulent material which has been swallowed from the nasopharynx. Small abscesses have been found on the borders of the eyelids; others at the bases of the nails, and, in one case, a large pus pocket was found embedded in the wall of the vas.

In regard to the multiple purulent onychia noted above, it should be mentioned that Haden and Jordan [9] have reported experimental work in which they claim that multiple onychia can be produced as a result of a blood borne infection having as a source septic foci in the teeth. Grieves [8] has found that such infective foci exist as a result of these defective diets. It would therefore seem probable that this case of multiple purulent onychia is an exceptional graphic demonstration of the generalized infection that affects many of these deficient rats.

Mention has been made elsewhere in the literature of the fact that normal rats, under laboratory conditions, occasionally develop a peculiar infection of the lungs that causes death. This condition is similar to that described above but is in less aggravated form and only occurs: (*a*) in old rats; (*b*) in those which have been subjected to too heavy a reproductive strain and, as a result, have their resistance lowered to a critical point, and (*c*) in those whose vitality was never on a par with that of their mates. Any change from the normal habitus of an animal will make it more susceptible to the inroads of disease, and, for that reason, only the most robust and vigorous should be selected for experimental purposes. It must not be forgotten that the same tendencies are inherent in vigorous animals, and that it takes only some additional load, such as a defective diet, to make the same diseases appear in them.

It will thus be seen how the decrease in the secretory elements of the eyes and mouth lowers the resistance to invading organisms which soon dominate the situation with serious results. Histologic sections of the trachea reveal a desquamated and eroded condition. In the lungs, the alveoli can be seen breaking down to form larger cavities. Wherever the lining of the alveoli is eroded or broken through, numerous organisms can be seen invading the surrounding tissue. This infection cannot be of pronounced virulence, for occasionally normal animals develop the snuffles and recover with no further extension of the infection. The

9. Haden, R. L., and Jordan, W. H.: Multiple Onychia as a Manifestation of Focal Infection, Arch. Dermat. & Syph. **8**:31-36 (July) 1923.

test rats become affected in the same degree as their diet is deficient. If the diet is only moderately deficient or if the animal is of greater vigor, the infection is overcome but recurs again and again with increasing severity as the deficiency becomes more and more pronounced.

The lung condition above described is decidedly at variance with another pulmonary involvement which also occurs but in which the pyogenic agency does not play so prominent a part. Rats dying of the latter condition do not run so long a course. The process is more fulminating and is not always associated with a metabolic decline; that is, their growth curves may still be on the ascent. They will, nevertheless, generally show slight pyogenic involvement at the base of the tongue or in the ears. The nose, however, instead of containing mucopurulent material, has a serosanguineous exudate which discharges quite freely from the nares. The tracheal mucosa is inflamed and covered with a sanguineous exudate. The lungs are extremely congested. This is evidently a bronchogenic pneumonia of a sufficiently virulent type to overwhelm the animal before much loss in body weight has occurred.

The fatalities resulting from the infections described in the foregoing are not due, according to Werkman,[10] to any reduction in the cataphylactic activity of the animal. Findlay [11] showed that in vitamin B deficient pigeons, the resultant loss in body heat was the decisive factor in the development of fatal pneumonias. In our animals, loss of heat could not have been a factor since their temperatures did not decline from the normal 101 to 102 F. for many days after the infection was obviously present. In fact, a drop in temperature was almost always associated with a slowing of the respiratory rate and the two together considered as early signs of death. We have frequently observed rats with a body temperature so low as not to be obtainable with an ordinary clinical thermometer and with respiratory rates of 16 to 20 a minute. Any influence of a possible resultant thrombopenia on susceptibility to infection cannot be claimed as the evidence is too conflicting.[12]

COMMENT AND SUMMARY

In general, the results of test feeding depend to a great extent on the time in a rat's life when the experimental dietary is commenced. We

10. Werkman, C. H.: Immunologic Significance of Vitamins; Influence of Lack of Vitamins on Production of Specific Agglutinins, Precipitins, Hemolysins and Bacteriolysins in Rat, Rabbit and Pigeon, J. Infect. Dis. **32**:247-254 (April) 1923.

11. Findlay, G. M.: B Vitamin and Pneumococcal Infection, Lancet **1**:714-715 (April 8) 1922.

12. Cramer, W.; Drew, A. H., and Mottram, J. C.: Behavior of Platelets in Vitamin A Deficiency and Technique of Counting Them, Brit. J. Exper. Path. **4**:37-44 (April) 1923. Bedson, S. P., and Zilva, S. S.: Influence of Vitamin A on Blood Platelets of Rat, Brit. J. Exper. Path. **4**:5-12 (Feb.) 1923.

wish to emphasize the fact that on this point depends whether or not the results noted are due to functional or to organic changes. If a rat is used for experimental feeding tests after it has attained its growth, the results will be more or less due to functional disturbances, while those obtained with rats that are fed test diets during the growing stage will be due to organic changes. Especially is this true of vitamin A underfeeding. A rat raised on a diet lacking only in vitamin A has a pluriglandular deficiency in substance as well as in secretion such that normality cannot be established by any increase in the vitamin A fraction. The best that could be expected on an optimal diet would be a maximum efficiency for what tissue it possesses. On the other hand, adult rats whose tissues have matured but are in a nonfunctioning condition because of the lack of these essential elements, can be restored to their original activity when the missing factors are supplied.

Stress is laid on the point that not only must a diet be adequate in all respects but that it must also be presented to the body at a time when its life's forces can utilize it in the formation as well as the operation of its cellular units.

The pathologic condition arising from vitamin A deficient diets has been described under two heads, primary and secondary. The primary change occurring is a generalized decrease in glandular activity resulting in xerosis of the eye, mouth, larynx and skin, and in malnutrition and sterility. This makes possible the secondary changes that occur, namely, those produced in the eye, nose, mouth and lungs by bacterial invasion.

THE RESPIRATORY ORGANS IN HEALTH AND IN DISEASE

XVIII. THE VITAL CAPACITY OF THE LUNGS IN CHRONIC FIBROUS PLEURISY, HEALED EMPYEMA AND PULMONARY TUBERCULOSIS BOTH CLINICAL AND NONCLINICAL *

J. A. MYERS, M.D.
AND
C. H. RICE, B.S.
MINNEAPOLIS

In an earlier study, it was stated that "groups of cases with evidence of parenchymatous lesions showed reduction in the average vital capacity. The average vital capacity was found to decrease with the extent of disease revealed by the roentgen-ray and physical signs. There was also a decrease in the average vital capacity with increase of symptoms." Since that time, considerable new data have accrued. As the data are treated somewhat differently in this study, we felt that it would be permissible to include some of those used in the earlier study. The vital capacity percentages were taken from tables [1] prepared from Dreyer's [2] weight formulas and West's [3] surface area method.

When 773 cases were grouped according to physical signs, 338 were found to be negative. This group of negative cases presented an average vital capacity of 102.4 per cent. of the theoretical normal. The average percentage of vital capacity previously reported [4] in 149 cases was 103.6 per cent. of the normal. These figures agree quite closely with those reported by others for persons ranging in age from 18 to 40 years. Most

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* Presented before the medical staffs of the Lymanhurst School for Tuberculous Children and the Parkview Sanatorium, June 24, 1924.

* From the department of internal medicine and the department of preventive medicine and public health, University of Minnesota Medical School, and the Parkview Sanatorium.

* This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

1. Myers, J. A.: Studies on the Respiration Organs in Health and Disease, VIII, A Method for Quickly Obtaining the Percentage of an Individual Theoretical Normal Vital Capacity of the Lungs, Am. Rev. Tuberc. **7**:161 (May) 1923.

2. Dreyer, Georges: Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227 (Aug. 9) 1919. Dreyer, Georges; and Hanson, G. F.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

3. West, H. F.: Clinical Studies on the Respiration, VI, A Comparison of the Various Standards for the Normal Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

4. Myers, J. A.: Studies on the Respiration Organs in Health and Disease, VII, A Correlation of Symptoms, Vital Capacity Readings and Physical and X-Ray Findings in 619 Cases Examined for Pulmonary Tuberculosis, Am. Rev. Tuberc. **6**:702 (Oct.) 1922.

of the cases presented in this study are within these age limits. In forty-seven of our cases, the diagnosis was reserved on first examination because the evidence was not sufficient to justify either a positive or a negative diagnosis. In Table 1, it will be seen that the average vital capacity for this group was 98.7 per cent. of the theoretical normal. When physical signs are present to justify a classification of minimal tuberculosis, ninety-eight cases with symptoms *A* present an average vital capacity of 90 per cent.; thirty-two cases with symptoms *B* present an average vital capacity of 81.3 per cent., while six cases with symptoms *C* present an average vital capacity of 77.4 per cent., of the theoretical normal.

Table 1 shows that when the physical signs justify diagnosis of moderately advanced and far advanced disease, the vital capacity is very materially decreased and the decrease becomes more marked with increase in symptoms.

TABLE 1.—*Seven Hundred and Seventy-Three Cases Grouped According to Symptoms and Physical Signs*

	Number of Cases	Average Vital Capacity
Negative	338	102.4
Diagnosis reserved	47	98.7
Pulmonary tuberculosis:		
Minimal A	98	90.0
B	32	81.3
C	6	77.4
Moderately advanced A	68	83.0
B	66	74.1
C	11	69.5
Far advanced A	34	53.0
B	52	50.7
C	21	42.6
Total	773	

In Table 2, 717 cases are grouped according to roentgen-ray findings. In 112 of these cases in which the stereoscopic plates revealed no evidence of disease, the average vital capacity was found to be 104.1 per cent. of the normal. When chronic fibrous pleurisy is present, it will be seen that the average vital capacity is approximately 10 per cent. lower than in the normal cases. A slightly greater reduction was found in twenty-six cases with healed empyema.

When lesions were revealed in the lung parenchyma, we did not possess a method of determining accurately the volume of lung tissue involved; therefore, the cases were grouped according to an estimated volume of involvement. Those with shadows "above the first rib" (Table 2) did not all have involvement of that total area, but many had small shadows scattered through that area. This also is true of the group of "not more than one lobe" cases. A case with small shadows through one lobe might, therefore, have a smaller total volume of involvement than one with heavy shadows above the first rib.

Another point of considerable interest to us is that many of the cases presented here did not have clinical tuberculosis; in other words, they fall into that group in Brown's [5] classification of demonstrable nonclinical cases. Many of them gave no history of illness. Of this entire group, some were examined because they were applying for insurance or compensation; some were examined because they believe in periodic physical examinations, and others were examined because they showed definite symptoms. Of the entire group of 717 cases, 203 fell into the "above the first rib" group. The average vital capacity for this group was found to be 98.7 per cent. of the theoretical normal. This figure is only slightly below that of 101 cases with negative roentgen-ray findings (Table 2).

TABLE 2.—*Seven Hundred and Seventeen Cases Grouped According to Roetgen-Ray Findings*

			Clinical Tuberculosis		Clinical Significance Questionable		Nonclinical Tuberculosis	
	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity
Negative	112	104.1	..	.....	..	.....	..	.....
Pleurisy (chronic fibrous)	54	94.1	..	.....	..	.....	..	.....
Empyema (healed)	26	91.0	..	.....	..	.....	..	.....
Pulmonary tuberculosis:								
A. Unilateral								
1. Above the first rib	203	98.7	42	85.5	9	89.0	152	103.0
2. Not more than one lobe	94	96.5	38	87.5	7	92.1	49	103.7
3. More than one lobe	22	65.6	22	65.6	None	.....	..	.....
B. Bilateral								
1. Above the first ribs	70	95.5	30	84.3	8	98.7	32	102.8
2. Not more than two lobes	90	80.9	69	74.4	4	106.0	17	104.8
3. More than two lobes	46	53.8	46	53.8	None	.....	..	.....
Total	717							

Of the 203 cases, however, only forty-two had clinical disease. Their average vital capacity was found to be 85.5 per cent. of the normal or more than 18 per cent. lower than the group of 101 negative cases. Of the 203 cases, there were nine in whom the clinical significance was questionable at the time of the examination. They presented an average vital capacity of 89 per cent. of the normal. Among the 203 cases, 152 fell into the class of demonstrable nonclinical disease. It was gratifying to us to find that this group possessed an average vital capacity approximately as high as the group of negative cases.

It is obvious, therefore, that it is never fair to the vital capacity test to present averages from cases grouped according to the roentgen-ray findings alone. The clinical significance of disease is of utmost importance. This holds true throughout the remainder of Table 2, which is

5. Brown, Laurason: Early Diagnosis of Pulmonary Tuberculosis, J. A. M. A. **78**:79-84 (Jan. 14) 1922.

self explanatory. Small areas of nonclinical disease affect the vital capacity of the lungs very little or not at all. On the other hand, our study leads us to believe that clinical tuberculosis practically always reduces vital capacity.

At this point, attention must be called to one of the pitfalls in vital capacity work. It is a well known fact that because of special previous development and training a considerable number of persons have vital capacities much greater than those indicated by our present normal standards. Such persons may present capacities which appear to be above the normal but which in reality are definitely reduced. Because of this fact, the vital capacity test can never be as useful as we should like to see it. In other words, our normal standards can never be made to cover these exceptional cases any more than normal weight standards can ever cover unusual and exceptional cases. In such cases, the vital capacity test is of great value if actual readings have been recorded while patients were in good health. At any subsequent examination, a definite reduction in the vital capacity is of no little significance. The following case illustrates this point:

REPORT OF CASE

A man, aged 25, examined while apparently in good health, had a vital lung capacity of 5,000 c.c., which was much beyond his theoretical normal. The physical and roentgen-ray examination revealed no evidence of a pathologic condition of the chest. A few months later, this man appeared for reexamination. This time his general appearance had changed. He looked ill. His vital capacity was 2,500 c.c.—just half of his capacity when in good health. Further examination revealed an extensive pleural effusion. To be sure, this was easily detected by other means, but one occasionally encounters conditions less easy to detect, in which the vital capacity renders a very distinct service in diagnosis.

In a few persons apparently in good health, the vital capacity is considerably below that which our present normal standards would indicate. Although no cause can be found, it remains persistently low. Here, again, vital capacity records previously made are of great value. Although this ideal will never be reached, it is gratifying to know that many institutions, both educational and industrial, are making vital capacity records of their students and employes as a matter of routine. Many practitioners of medicine are also making records of the vital capacities of their patients. The recording of vital capacities probably will never become universal any more than the recording of body weights is universal; therefore, we will be compelled to use theoretical normal standards to a large extent. We wish to encourage the recording of vital capacity as a routine matter in just as many persons as possible, as we are convinced that the test is worth while, and that serial readings bring out the greatest value of the test to the physician.

NEPHROSIS

A CLINICAL AND PATHOLOGIC STUDY *

JOSEPH KAUFMANN, M.D., AND EDWARD MASON, M.D.
MONTREAL

The term nephrosis, introduced several years ago, was carefully studied by Volhardt, and later elaborated in the studies of Epstein, Eppinger and many other observers.

There is a type of disturbance in which one finds, as outstanding features, massive edemas and anasarca, low blood pressure, abundance of albumin in the urine, a urine of a high specific gravity, a urinary sediment that is rich in casts and shows a persistent absence of blood, and a kidney that shows essentially a degenerative process in the epithelial cells. This condition is clinically referred to as nephrosis. Further, we find that the urine contains globulin; there are no eye changes in the uncomplicated cases, the fundi remaining normal throughout the illness; there is a moderate but progressive anemia and an inability to excrete salt; the level of the plasma chlorids depends on the developing or eliminating of the edema; there is normal excretion of nitrogen end-products, normal blood nonprotein nitrogen, increase of cholesterol in the blood, a decrease in the total blood proteins, with a relative increase in percentage of globulin; edema fluids are rich in globulin, and there is a low basal metabolism (calculated on the false weight).

The foregoing clinical features might be considered as typical of a pure form of the condition from beginning to end, and establishes Type 1 of uncomplicated nephrosis.

CASE 1.—*Type 1 Nephrosis.*—R. E. B., a man, aged 29, was admitted to the Royal Victoria Hospital, Oct. 22, 1923, and died, Feb. 17, 1924. He was a farmer, and had been overseas, in France, four years during the World War.

He complained of swelling of the abdomen, legs and back, coughed, and had pain in his sides.

He had suffered with pyorrhea and bad teeth for several years preceding the onset of the present illness. He was in a hospital, in France, with this trouble, on one occasion for eight days, and on a second occasion for fourteen days. He was a chronic sufferer from sore throat. July 16, 1923, after the extraction of several teeth, he first noticed a painless swelling of the external genitalia, which was later followed by swelling of the legs and back. He also had some headache. His appetite became poor. The swelling of the limbs became annoying. There was some frequency of micturition by day, but no night frequency. No disturbances of vision were noted. About the middle of September, the abdomen became greatly swollen, and he was very short of breath.

The patient had had no venereal disease. He was a moderate smoker, and did not use alcoholic beverages. He had been a hard laborer all his

* From the Royal Victoria Hospital.

life. He had had measles, whooping cough and chickenpox in early childhood. The family history was good.

Examination showed a well-developed man of good color, weighing 180 pounds (81.6 kg.), with marked edema of the legs and thighs; ulcerated and decayed teeth; pyorrhea alveolaris, with evidence of abundant free fluid in the peritoneal cavity. The liver and spleen were of normal size. There was slight passive congestion of both lungs and moderate double hydrothorax. There was a slight pericardial effusion; otherwise, the heart was normal. The systolic blood pressure varied from 142 to 122; the diastolic, from 98 to 90.

Blood examination revealed: October 23, red blood cells, 5,400,000; white blood cells, 11,500; hemoglobin, 95 per cent.; November 3, red blood cells, 5,300,000; white blood cells, 10,000; hemoglobin, 85 per cent.; December 15, red blood cells, 5,100,000; white blood cells, 9,200; hemoglobin, 80 per cent.; Jan. 28, 1924, red blood cells, 4,720,000; white blood cells, 10,600, and hemoglobin, 75 per cent. The blood smear was normal.

The blood Wassermann reaction was negative, even after a provocative dose of neoarsphenamin. The prostate showed a simple enlargement. The remaining systems showed nothing of importance.

The urine was turbid amber; specific gravity was 1.032; the albumin totaled from 5 to 8 gm. a liter. Microscopic examination showed coarse and fine granular and hyaline casts. A phenolsulphonephthalein test resulted in the return of 34 per cent. in the first hour, and 14 per cent. in the second

TABLE 1.—*Blood Chemistry in Case 1*

Date	Blood Urea, Gm. per Liter	Creatinin, Mg. per 100 C.c.	Plasma Chlorids, Gm. per Liter	Fundi
10/23/23	0.39	1.5	5.97	.....
10/27/23	0.46	....	6.22	.....
12/18/23	0.31	1.75	....	Normal
1/ 4/24	0.24	1.52	6.138	.....
1/11/24	0.29	1.47	6.47	.....
1/29/24	0.37	1.55	6.14	.....

Nov. 5, 1923: globulin, 2.25 per cent.; albumin, 3.48 per cent.

hour, a total of 48 per cent. in two hours. This test was repeated and always showed a good output.

Jan. 12, 1924, the concentration of urea was 1.8 per cent. in the second hour, and the factor, determined according to McLean, was 31.6 (slightly lowered).

January 7, the ascitic fluid showed 6.14 gm. sodium chlorid per liter.

The Mosenthal test showed a fixed specific gravity of the urine at 1.020. The electrocardiogram showed a normal tracing. The basal metabolism was minus 20 per cent. (estimation on false weight). A roentgen-ray examination of the chest showed fluid at the bases of both lungs.

The ordinary intake of fluids had varied from a minimum of 600 c.c. to a maximum of 1,300 c.c. The output varied from 2,030 c.c., early after admission, to almost anuria, just before the patient's death.

The temperature was normal, except toward the end, when he developed a terminal pneumococcic peritonitis, from which he died.

The abdomen was aspirated six times between November 27 and February 12, a total of 25,260 c.c. of fluid being withdrawn, varying in color from a clear straw to turbid, and containing lymph flakes.

The patient's condition went from bad to worse. He developed a pneumococcic peritonitis, Feb. 12, 1924, and died some five days later of respiratory embarrassment. There was no coma. Therapeutic measures, consisting of various diets and drugs, were all of no avail, and did not modify the course of the illness.

The following is a brief summary of the positive findings which have a definite bearing on the case: The onset was that of a renal disease with

gradually increasing edema and anasarca. The heart and blood vessels were normal. The blood pressure was normal. The urine showed a moderately high and fixed specific gravity and high albumin content, with abundance of casts but no blood. There was some secondary anemia. Blood chemistry showed a slight chlorid retention; otherwise, the findings were normal. The ratio of albumin to globulin in the blood was normal. The phenolsulphonephthalein output was only slightly impaired. The fundi were normal. Basal metabolism was low. The gums and teeth were diseased. Therapeutic measures were disappointing. The patient died with a terminal pneumococcus infection of the peritoneal cavity. There was no uremia. There were no signs of ruptured compensation.

The postmortem examination showed the following findings: degenerative and exudative nephritis, and pneumococcic peritonitis.

Other lesions were: parenchymatous degeneration of the organs; hyperplastic splenitis; hydrothorax; hydropericardium, and anasarca.

Macroscopic examination of the kidneys revealed that the left kidney weighed 300 gm. and the right kidney, 270 gm. In both kidneys, the capsule stripped with ease, leaving a smooth, pale surface with vascular markings. On section, the cortex bulged slightly and appeared swollen. The differentiation between the cortex and the medulla was fair. The surface showed reddish and yellow radiating streaks. The medulla was yellowish and appeared fatty.

When microscopic examination was made, the glomeruli appeared to be intact. The lumina of the tubules were dilated and filled with pale staining structureless material. Some of the tubular epithelium had desquamated, while the rest was granular and hazy in outline. The whole section appeared edematous, with an increase in size of the spaces between the tubules. There was little or no inflammatory exudate, and no increase in fibrous tissue. The blood vessels were dilated and filled with blood.

The second type of the same disease is one which, while retaining certain of the features of Type 1, has certain alterations as well as additions to the clinical picture. The blood pressure rises moderately; fundi changes develop, and the patient loses the ability to concentrate the urine (as in Type 1). There is an impairment in nitrogen excretion, and fat appears in the urine and ascitic fluid. Among the features of Type 1 which are retained are: massive edema and anasarca; poor chlorid excretion; high cholesterol in the blood and high plasma and transudate chlorids.

Case 2.—*Type 2 Nephrosis.*—J. A. L., a man, aged 53, was admitted to the Royal Victoria Hospital Jan. 4, 1924, and died February 16. He was a laborer, and had been in overseas service, in France, three years during the World War. His complaints were swelling of the abdomen, legs and arms, with headache, weakness and dry mouth.

In June, 1918, the patient was invalided home from France on account of so-called chronic rheumatism. He worked very hard until December, 1921, but noticed during that time that his legs were swollen and that he was short of breath. Late in December, 1921, he was obliged to give up work because of these complaints. In January, 1922, he was admitted to the Western General Hospital, and remained there for five months, the condition having progressed. The abdomen and scrotum now became swollen, and he complained of great thirst and a dry mouth. Since leaving the hospital, he had been a confirmed invalid, although he was able to go for moderate walks. In December, 1922, he was readmitted to the hospital, and remained there for three months, without making any favorable progress. He left the hospital in February, 1923. He now complained of headaches more or less constantly. November,

1923, he took to bed on account of the increasing swelling of the legs. Jan. 4, 1924, he was admitted to the Royal Victoria Hospital. He was short of breath, complained of palpitation, coughed a good deal and vomited frequently. He had some night and day frequency.

The patient had had diphtheria, measles and whooping cough in childhood. He was a moderate smoker, and had been a heavy drinker of beer until 1920 (drinking from ten to fifteen glasses daily), but not since then. He said he had had no venereal disease. He had had rheumatism in the joints and muscles in 1918 (not acute rheumatic fever).

The father of the patient suffered from renal calculus, being 89 years old. The mother died of chronic interstitial nephritis at 36. The family history was otherwise negative.

Examination showed a well developed, large man, with pale skin and mucous membranes, marked edema of the legs and thighs, bad teeth and healthy gums. There was massive effusion into the peritoneal cavity and extensive edema of the abdominal wall. The rectum and the prostate were healthy. The liver and spleen were not palpated. There was some congestion of the lungs with double hydrothorax, slight hypertrophy of the heart and pericardial effusion. The systolic blood pressure varied from 194 to 170, the diastolic from 108 to 110. The blood showed a well marked secondary anemia with some anisocytosis and poikilocytosis. The differential blood count was normal.

TABLE 2.—*Blood Chemistry in Case 2*

Date	Blood Urea, Gm. per Liter	Creatinin, Mg. per 100 C.c.	Plasma Chlorids, Gm. per Liter	Fundi
1/11/24	0.95	2.61	7.11	Albuminuric retinitis
1/24/24	1.03	3.15	6.62	.....
2/13/24	1.56	3.61	....	.....

Carbon dioxid capacity, 16 per cent. by volume. Blood proteins: total nitrogen, 0.77 per cent.; nonprotein nitrogen, 0.13 per cent.; globulin, 1.44 per cent.; albumin, 3.06 per cent.

Blood examinations revealed: January 20, red blood cells, 3,020,000; white blood cells, 13,400; hemoglobin, 60 per cent.; January 25, red blood cells, 3,200,000; white blood cells, 9,750, and hemoglobin, 45 per cent. The blood Wassermann reaction was negative. The fundi showed a well marked albuminuric retinitis. The remaining systems showed nothing of importance.

The urine was dark amber; acid; the specific gravity was 1.022; the albumin +++. Microscopic examination revealed granular and hyaline casts, fat globules and a few pus cells. No blood was seen microscopically or chemically. A phenolsulphonephthalein test resulted in a return of 7 per cent. in the first hour, and 5 per cent. in the second hour, a total of 12 per cent. in two hours. This test was repeated, a few days later, and showed a total output of 14 per cent. in two hours.

The electrocardiogram showed a right sided preponderance.

Examination of the ascitic fluid revealed: specific gravity, 1.020; a trace of albumin; globulin +, and chlorids +. A second paracentesis, eight days later, showed that the fluid in the main was the same, except that it contained a moderate quantity of neutral fat.

Cholesterol in the blood totaled 555 mg. per hundred cubic centimeters. Ascitic fluid chlorids totaled 7.61 gm. sodium chlorid per liter. The urea concentration and factor showed marked impairment.

There was a decrease in the total plasma proteins. The albumin-globulin ration was normal. The basal metabolism was minus 24.5 per cent. (estimation on false weight). Roentgen-ray examination of the chest showed the heart transverse and moderately large. The ordinary intake of fluids varied from

775 c.c. to 1,200 c.c., and the output varied from 1,450 c.c. to almost a complete anuria just before death. The temperature was normal during his entire stay in the hospital, in spite of the fact that, during the last ten days, he had a marked acute otitis media. The abdomen was aspirated three times between January 5 and 18. Fifteen thousand four hundred cubic centimeters of opalescent and at last almost milky fluid were withdrawn.

The patient's condition grew progressively worse. Therapeutic measures gave no relief whatsoever. The patient became uremic toward the end and died in coma.

The following is a brief summary of the positive findings, which have a definite bearing on this type of nephrosis: The onset was that of renal disease of some two years' standing with gradually increasing edema and anasarca; the heart showed some hypertrophy, and the blood pressure was elevated. Albuminuric retinitis was present. The urine output was moderate; the specific gravity was fixed; albumin was always abundant, and the sediment contained abundant hyaline and granular casts and fat, but no blood. The phenolsulphonephthalein output was greatly reduced. There was a marked retention of urea and creatinin; the chlorids in the blood were high; the chlorids and globulin in the ascitic fluid were high and the cholesterol in the blood was high. The ascitic fluid and urine contained neutral fat. The basal metabolism was low. There was a marked secondary anemia. There was a terminal acidosis. Therapeutic measures were of no avail. The patient developed uremia and died in coma. There were no signs of ruptured compensation. The postmortem examination was made one hour after death, and a report was returned of degenerative and productive nephritis. The subsidiary lesions were: arteriosclerosis, hydrothorax, hydropericardium, ascites, anasarca and a terminal right upper lobar pneumonia.

Macroscopic examination of the kidneys revealed that the left kidney weighed 120 gm.; the right kidney, 140 gm. The renal arteries were intact. The capsule stripped easily and showed a smooth surface of pale yellow. On section, the cortex bulged slightly and was pale in color, and the differentiation was poor. The cortex was narrow, 0.5 cm., with much peripelvic fat. Both kidneys showed the same condition.

Microscopic examination showed that many glomeruli were shrunken. Some showed synechiae, partial or complete. There was considerable edema of the tissues between tubules, with some fibrous tissue production. The tubules showed dilated lumina with low epithelium and many hyaline casts. Blood vessels were thickened, especially in the intima, and all were congested.

The third type represents all the stages of the disease.

Case 3.—*Type 3 Nephrosis, Showing in Early Part of Illness Characteristic Picture of Type 1, and in Terminal Part, Picture of Type 2.*—T. C., a man, aged 18, who had recently arrived from China, was admitted to the Royal Victoria Hospital, May 21, 1920, and died, Nov. 29, 1922. He remained in the Royal Victoria Hospital under constant observation from the early onset of his illness until his death, with the exception of a few short intervals during which he was allowed to return to his friends. The complaints were swelling of the legs, body, hands and face, with weakness.

Following an attack of some febrile disturbance about one month before admission, the patient noticed that his feet began to swell. The swelling progressed rapidly up his trunk, arms and face, and he was obliged to give up work. There were absolutely no other symptoms or signs in the early development of his illness. He had been ill with boils on the neck, while in China, some years before; otherwise, his history was good. There had been no past illness of any importance. The family history was excellent.

Examination showed a poorly developed young Chinaman, very pale, weighing 153 pounds (69.4 kg.), with marked generalized edema, ascites and hydrothorax. Fifty per cent. of the weight was fluid, as shown later by the true

weight when the edema was eliminated. The liver and the spleen were of normal size. The buccal cavity was healthy, and the heart was healthy. The systolic blood pressure was 110, the diastolic 65.

Urine examination gave specific gravity, 1.037-1.040; albumin, + + +, as high as 24 gm. per liter. The sediment was rich in casts; there was no blood. Oliguria was present day and night. There was an inability to excrete chlorids. The plasma chlorids were 5.8 gm. per liter. The nonprotein nitrogen in the blood was normal. The urea was 0.39 gm. per liter. The abdomen was tapped on several occasions, large quantities of clear, serous fluid being removed. On admission, the total plasma nitrogen was 0.74 per cent. The blood globulin was 2.08 per cent. and the albumin, 1.40 per cent. (reversed ratio).

Without any apparent reason, the anasarca began to clear gradually without any change in the albumin-globulin ratio. The blood pressure remained normal. The fundi were normal. July 28, 1920, the patient's weight, after the edema and anasarca had entirely disappeared, was 79 pounds (35.8 kg.) approximately half of what it was on admission.

The blood findings, when the anasarca was all gone, were as follows: total plasma nitrogen, 1.11 per cent.; nonprotein nitrogen, 30 mg. per hundred cubic centimeters; globulin, 3.4 per cent., and albumin, 2.7 per cent.

In spite of the disappearance of the anasarca, there was still a considerably greater amount of globulin than albumin in the blood.

During the stage of disappearance of the edema, the patient had a marked diuresis, as much as 2,700 c.c. of urine a day. When the diuresis started, the chlorids in the blood rose to 7.05 gm. a liter (July 5, 1920). When the diuresis was completed, the chlorids in the blood were down to 5.9 gm. a liter. The cause of the clearing of the edema was unknown. The patient failed to respond to all methods of treatment. With the onset of the illness, the chlorid output was less than 1 gm. a day. When the edema was disappearing, he was putting out from 15 to 16 gm. of chlorid a day. During all this time, he was never given salt as such; the food containing roughly about from 1 to 2 gm. of chlorids. He remained free from the edema for approximately three weeks, and, with apparently no cause, it recurred in the first week of August. Oliguria became a marked feature again; chlorid excretion dropped to 1 gm. a day.

Plasma chlorids were 5.8 gm. a liter, as at the onset of the illness.

The urine contained 30 gm. of albumin to the liter and the other features were the same as at the beginning. The systolic blood pressure was 110, the diastolic, 70. The proteins in the blood were: total plasma nitrogen, 0.91 per cent.; globulin, 3.61 per cent., and albumin, 1.29 per cent.

As advised by Epstein, the patient was now fed on a high protein diet, 1,548 calories with 70 gm. of protein. Previously, the diet had been kept at from 30 to 35 gm. of protein. The calories given were largely in carbohydrate. The high protein diet resulted in nitrogen retention, the blood urea rising to 0.6 gm. a liter. With the rise in the blood urea, the blood pressure rose also, the systolic being 130. The fundi remained normal. At this time, the albumin-globulin ration was 1:1. The blood cholesterol was 500 mg. per hundred cubic centimeters.

By the fall of 1921, the case presented features of nitrogen retention as well as chlorid retention, with greater inability to concentrate. The specific gravity kept at about 1.015. At this time, a definite creatinin retention developed, 2 mg. per hundred cubic centimeters of blood.

Throughout the first half of 1922, the edema continued to fluctuate, the blood pressure gradually rising to a level of 180 systolic, 110 diastolic.

Creatinin retention developed to 5 mg. per hundred cubic centimeters of blood. The plasma chlorids remained at from 6.2 to 6.5 gm. a liter. Inability to concentrate became more marked, ranging from 1.010 to 1.012. The casts

and albumin stayed as before. The albumin-globulin ratio was normal. The anemia progressed. The red blood cells totaled 2,000,000, with hemoglobin, 50 per cent.

In the fall of 1922, the patient developed an acute bronchitis, which failed to clear up, and which was subsequently diagnosed as miliary tuberculosis. Death occurred, November 29, with a marked acidosis of 36 per cent. by volume carbon dioxid (capacity).

It is interesting to note that this patient, in September, 1920, developed a renal glycosuria, having from 5 to 8 gm. of glucose a day in the urine until death. At no time did the blood sugar rise above a normal figure, the average value being 0.08 per cent.

The following is a brief summary of the important findings in this case: The early stage of the illness clearly resembled Type 1. The findings were:

1. Edema and general anasarca.
2. High and fixed specific gravity of the urine, which was very rich in albumin and in which the sediment contained a large number of hyaline and granular casts, but no blood.
3. Low blood pressure; the heart and blood vessels were normal.
4. A secondary anemia.
5. Blood chemistry showing a chlorid variation according to whether the edema progressed or diminished. Normal nonprotein nitrogen, with the globulin in the blood nearly twice the amount of albumin.
6. The fundi were normal.
7. Basal metabolism was low.

With the progress of the disease, other features developed closely resembling the well defined stages of Type 2:

1. Rising blood pressure.
2. Nitrogen retention.
3. Return of albumin-globulin normal ratio in the blood.
4. Retinal hemorrhages.
5. More marked anemia.
6. The urine showed a lowered specific gravity, the albumin and sediment remaining about the same. There was no blood.
7. The chlorid retention improved somewhat with the development of the nitrogen retention.
8. There were no signs of cardiovascular give way.

The following points are of special interest in connection with this case:

1. The disappearance of the edema without the alteration of the blood proteins.
2. The high protein diet resulted in nitrogen retention.
3. No red blood cells were found in the urine at any time.
4. Starting with a low blood pressure and a high urinary concentration, as the months passed, the blood pressure rose and inability to concentrate progressed.
5. Anemia progressed without remission.
6. The occurrence of renal glycosuria.
7. The immediate cause of death was an intercurrent infection.

The postmortem examination resulted in the following report: Productive nephritis (small white kidneys); generalized miliary tuberculosis (lungs, spleen, liver, kidneys, suprarenals, pancreas, bladder and peritoneum) and tuberculosis of mediastinal glands; edema, ascites and hydrothorax. There were numerous minor findings of no bearing on the case.

Macroscopic examination of the kidneys showed that the left kidney weighed 60 gm. The vessels were not markedly arteriosclerotic; the capsule was opaque, the cut surface was pale and greyish yellow; the cortex and medulla

were poorly marked; the cortex was very narrow; vascular markings were lost; the capsule was only slightly adherent, and when stripped left a moderately finely granular surface, studded with fine miliary tubercules. The right kidney was small, weighing 55 gm., of regular shape; the capsule was stripped easily, leaving a slightly rough surface studded with fine tubercles. The cut surface was pale; vascular markings were slightly more prominent than in the left kidney. The cortex was narrow, and in the periphery were several fused small areas between radiating vessels.

In the microscopic examination of the kidneys, the sections showed very widespread productive lesions; changes in the glomeruli were marked and showed all stages of thickening of the capsule, fibrosis and atrophy of the tufts of connective tissue between the tubules which, however, were more marked in some areas, producing a slight island appearance. Many of the tubules contained casts, hyaline, granular or cellular. The epithelium lining the tubules showed varying stages of granular degeneration. Definite scattered tubercles also were seen showing typical epitheloid proliferation, slight or early central necrosis and a very marked peripheral round celled infiltration.

A brief clinical study of this case shows conclusively that in the early stage of the illness the patient suffered from a typical nephrosis resembling in most details that of Type 1. In the later and last stages of the illness, the picture changed somewhat; while still retaining some of the features of Type 1, there were definite evidences of clinical changes and blood chemistry of Type 2. In short, we have both types well and clearly exemplified in one patient, showing that if the patient lives long enough, one type of the disease will progress into the second type and the gross and microscopic changes in the kidneys will go hand in hand with the clinical progress and blood chemistry alterations. We are dealing in this case, then, with one disease entity, both in its early and in its later stages, the kidney changes being merely evidences of a later stage of the organ in the progress of the illness. It would seem that the condition of the kidney depends essentially on the supervention of the intercurrent fatal infection.

SIMILARITY OF TYPES

A careful clinical study of our cases reveals the following points of interest in all of them:

1. The edema was massive, and one may say that an early general anasarca was the rule. All cases had effusion into the potential serous cavities.

2. Albumin in the urine was very abundant, going up to 30 gm. a liter.

3. The specific gravity was, generally speaking, high in the early stages, progressing to a low level as contraction of the kidney developed.

4. Blood was absent in the urine.

5. Urinary sediment was rich in casts, especially of the hyaline and granular varieties.

6. The output of urine was small, as a rule, always less than 1,500 c.c., save when powerful diuretics were used, and even then seldom exceeded 2,500 c.c. on more than one or two occasions.

7. Chlorids in the urine were low.

8. Plasma chlorids fluctuated according to the degree of anasarca present.

9. Urea and nitrogen disturbances in the blood and urine were not much affected when the principal feature of the disease was the nephrosis of Type 1. With contraction of the kidneys (Type 2), nitrogen retention developed.

10. Fundi were normal in early cases, but hemorrhages and retinitis were encountered in the later stages.

11. The early cases showed a normal or low blood pressure, while the late forms showed high blood pressure.

12. All our cases had few or no objective or subjective signs of cardiac embarrassment, nor did the postmortem examination show evidences of a failing cardiovascular system.

13. Cholesterin in the blood was increased, and neutral fat was present in the ascitic fluid and urine.

14. Therapeutic results were only temporarily beneficial.

Pure forms of nephrosis, the so-called textbook picture, are uncommon. Combination forms, with productive or exudative changes superadded, are more common. The combination forms usually have a high blood pressure, albuminuric retinitis and urea retention. When the nephrosis is the important feature, we find that the specific gravity of the urine is fixed and at a higher level, and albumin is more abundant than one finds in the kidneys in cases of chronic nephritis or of heart disease. In the combination forms, we find the edema very early, and we cannot attribute it to the defective cardiac function.

COMMENT

Is nephrosis a renal disease entity, or is it a local manifestation of a general systemic disturbance?

It would appear that the edema has little relation to the kidneys, but that it depends on an altered state of capillary permeability. The cause of this increased permeability is unknown. It may be toxic or it may be nutritional. We believe that nephrosis, as applied to the kidneys, is an early manifestation of a general systemic cellular degenerative process of unknown origin.

It is interesting, in this connection, that these patients show a lowered basal metabolism, which would have to be classified as a secondary hypothyroidism. Their thyroids can manufacture thyroxin at a normal rate, but, due to the lack of tissue call, the thyroxin content of the tissues falls below normal. This results in altered cellular nutrition.

The evidence at our disposal indicates that the true nephrotic kidney progresses into the secondary contracted type as a result of an organizing process of the degenerated cells, and not as a primary inflammatory entity.

The pathologic findings, in the different cases, vary according to the stage in the disease at which death occurs.

THE EXCRETION OF ORGANIC ACIDS AFTER PNEUMONIA *

S. W. CLAUSEN, M.D.
ST. LOUIS

In this paper, it will be shown that large quantities of organic acid are excreted in the urine after the crisis in pneumonia.

The patients studied ranged in age from 16 months to 14 years. Eight were typical lobar pneumonia patients; two had bronchopneumonia following influenza. The total quantity of urine in twelve hours was collected, preserved with toluene and kept on ice until analyzed. Analytic methods were: (*a*) determination of total organic acids by the method of van Slyke and Palmer,[1] and (*b*) the determination of ether soluble acids by the following method: Two cubic centimeters of urine was placed in a test tube; 1 gm. of solid ammonium sulphate and 1 drop of concentrated sulphuric acid were added. The ether soluble acids were removed in the continuous ether extractor recently described.[2] Occasionally emulsions formed, and the results of analysis were liable to be too high. No result was accepted when sulphate could be demonstrated in the ether extract by means of barium chlorid. The ether extracts in the Kjeldahl flasks were evaporated to a small volume and titrated with carbon dioxid—free twentieth normal sodium hydroxid. The results of all analyses are expressed in terms of tenth normal acid.

Data are presented in the tables which give the patient's weight, the date of onset and the duration of the pneumonic process. The columns in the tables give date, volume of urine, acid as determined by van Slyke's method, ether soluble and ether insoluble acid (determined by difference) and the maximum daily temperature. It will be seen that the excretion of organic acid is considerably in excess of the normal figure (from 8 to 11 c.c. per kilogram a day) given by van Slyke. The maximum excretion of organic acid occurs from one to four days after the crisis. In cases of lysis (Case 10, E. W.), the maximum is not strikingly high. In certain other cases, however, the maximum is exceedingly high (from three to eight times the normal). It will be seen that this maximum corresponds only roughly to the period of

* From the department of pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Van Slyke, D. D., and Palmer, W. W.: Titration of Organic Acids in Urine, J. Biol. Chem. **41**:567 (April) 1920.

2. Clausen, S. W.: A Method for the Determination of Small Amounts of Lactic Acid, J. Biol. Chem. **52**:263 (May) 1922.

maximum diuresis. In general, the maximum excretion of ether soluble acids coincides with that of the ether insoluble acids. It is to be noted, however, that ether insoluble acids comprise by far the greatest part of this maximum excretion. Furthermore, the period of maximum excretion corresponds to the period of resolution of the pneumonic process, as determined clinically.

Efforts are being made to determine the nature of the ether insoluble acids. The nature of the ether soluble acids also is as yet undetermined. It is likely that acetone body acids make up only a small proportion of the total, the ferric chlorid reaction in most cases being only slightly positive and then only during the febrile stage.

In order to get some idea of the nature of the ether soluble acids, use was made of their distribution ratio between water and ether. The ether extract from a considerable quantity of urine was titrated with saturated barium hydroxid; any precipitate (containing such barium salts as the sulphate, carbonate, phosphate or oxalate) was removed by filtration. The filtrate was evaporated to a small volume, and reextracted with ether. This second extraction was performed in steps, adding at each step one fifth of the quantity of sulphuric acid calculated to neutralize the entire amount of barium. It is obvious that those acids which are "weaker" will be liberated first; since these are, in general, more readily soluble in ether, the successive fractions will represent a fairly good separation. Each ether extract was shaken with water at 20 C., and the concentrations of acid in the water and in the ether were determined by titration with the carbonate-free twentieth normal sodium hydroxid. The concentration in ether will, under these circumstances, depend only on the concentration in the water, and will be independent of the total quantity of water, ether or acid, and will be affected only slightly by small amounts of other substances. Moreover, the ratio of concentrations is nearly, but not quite, independent of the actual concentrations. By this procedure, it is possible to demonstrate in normal urine and in the urine from patients with pneumonia, at least two ether soluble acids.

TABLE 1.—*Ratio of Concentrations*

	Extract Number 1	Extract Number 2	Extract Number 3	Extract Number 4	Extract Number 5
Normal Urine:					
Molar concentration in ether	0.024	0.0192	0.0295	0.0078	0.001?
Molar concentration in water	0.067	0.057	0.075	0.053	0.0065?
Ratio	0.36	0.33	0.168	0.148	0.15?
Pneumonic Urine:					
Molar concentration in ether	0.015	0.0118	0.0126	0.0062	.....
Molar concentration in water	0.040	0.0566	0.102	0.049	.....
Ratio	0.375	0.208	0.124	0.126	.....

Acids with distribution ratios near those found for urinary acids in the concentration range in question are: citric acid, with a ratio of 0.023; lactic acid, with a ratio of 0.10; formic acid, ratio, 0.12; oxalic acid, ratio, 0.13; betahydroxybutyric acid, 0.40; acetic acid, 0.47; propionic acid, 1.8, and n-butyric acid, 3.4.

TABLE 2.—*Findings in Case 1*

Weight, 10 kg.; onset, February 7; crisis, seventh day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 12	620	266	31	235	40.4
February 13	730	242	43	199	40.2
February 14	535	230	44	186	39.8
February 15	540	418	63	355	38.6
February 16	1,160	308	50	258	38.7
February 17	435	321	19	302	38
February 18	555	127	23	104	38
February 19	510	118	33	85	38.8

TABLE 3.—*Findings in Case 2*

Weight, 25 kg.; onset, February 17; crisis, seventh day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 24	154	210	18	192	40.2
February 25	340	496	74	122	38
February 26	350	1,188	41	1,147	37
February 27	187	469	32	437	37.5
February 28	500	210	26	184	38

TABLE 4.—*Findings in Case 3*

Weight, 20 kg.; onset, February 1; crisis, sixth day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 7–8	700	241	71	170	39.5
February 8–9	585	221	57	164	37.4
February 9–10	515	300	80	220	37.1
February 10–11	910	389	100	289	36.8
February 11–12	1,155	512	66	446	37
February 12–13	520	282	32	250	37.6

TABLE 5.—*Findings in Case 4*

Weight, 56 kg.; onset, February 15; crisis, sixth day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 20	1,900	834	210	624	40.2
February 21	1,260	755	155	600	39
February 22	1,760	740	158	582	38
February 23	2,670	1,330	193	1,137	37.8
February 24	2,140	960	148	702	37.6
February 25	820	514	160	354	37.6
February 26	260	187	32	155	37.6
February 27	1,380	762	186	576	37.6
February 28	830	252	51	201	37.6
March 1	1,070	369	63	306	37.5
March 2	1,460	850	190	660	37.4

TABLE 6.—*Findings in Case 5*

Weight, 22 kg.; onset, February 6; crisis, fourth day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 9	205	351	140	215	40.4
February 10	458	340	54	286	39.3
February 11	340	165	35	130	37.8
February 12	300	189	52	137	37.5
February 13	460	564	58	506	37
February 14	360	457	128	329	37.2

TABLE 7.—*Findings in Case 6*

Weight, 23 kg.; onset, February 1; crisis, seventh day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 7-8	270	236	14	222	40.6
February 8-9	258	245	46	199	38.6
February 9-10	253	484	73	413	36.8
February 10-11	918	593	71	522	36.8
February 11-12	555	412	78	334	37

It will be seen that the ether soluble acids in pneumonic urine may include formic, lactic, betahydroxybutyric, acetic, and probably others. Any oxalic acid present would have been precipitated by the barium hydroxid. Direct determinations show the absence of any large quantity of lactic acid in the urine in these cases.

TABLE 8.—*Findings in Case 7*

Weight, 22.7 kg.; onset, February 1; crisis, sixth day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 8	550	335	57	268	37.6
February 9	115	213	26	187	37.2
February 10	310	554	53	501	37.4
February 11	920	470	114	356	37
February 12	655	318	90	228	37.1

TABLE 9.—*Findings in Case 8*

Weight, 8 kg.; onset, February 22(?); crisis, seventh day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 27	225	154	23	131	39.2
February 28	250	590	32	558	39.4
March 1	200	634	24	610	38.2
March 2	102	96	12	84	37.8
March 3	210	89	13	76	37.2
March 4	80	120	6	14	38.2

TABLE 10.—*Findings in Case 9*

Weight, 6 kg.; onset, February 20; crisis, fifth day.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 24	370	86	20	663	40
February 25	675	390	117	273	38.8
February 26	340	290	48	242	36.4
February 27	400	223	46	187	36.8
February 28	350	138	21	117	37.8
March 1	220	153	30	123	38.6

TABLE 11.—*Findings in Case 10*

Weight, 30 kg.; onset (?); no crisis.

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 25	1,000	498	110	388	38.8
February 26	440	433	56	376	38.6
February 27	1,100	477	113	333	38.2
February 28	1,420	500	68	432	37.8
March 1	970	372	44	328	37.4
March 2	510	240	25	215	37.6
March 3	980	390	103	287	37.4
March 4	560	330	55	275	37.2

CONCLUSIONS

1. Large quantities of organic acids are excreted in the urine after pneumonia.

2. The period of maximum excretion corresponds to the period of resolution.

3. The larger part of the organic acids excreted during resolution in pneumonia is insoluble in ether.

THE ALKALINE TIDE IN ACHLORHYDRIA*

ROGER S. HUBBARD, PH.D.
AND
SAMUEL A. MUNFORD, M.D.
CLIFTON SPRINGS, N. Y.

It has been generally believed that the changes in the reaction of urine which occur after a meal are due to the secretion of hydrochloric acid by the stomach and its subsequent reabsorption in the intestines. This view has been opposed by Hasselbalch [1] and by Leathes,[2] but has been supported by the more recent work of Campbell [3] and Fiske.[4] The earlier literature has been reviewed in these articles, in an article by us,[5] and in a discussion of the acid-base balance by Wilson;[6] therefore, it does not seem necessary to discuss it again at this time.

The method of fractional gastric analysis proposed by Rehfuss, Bergeim and Hawk,[7] in 1914, has recently been subjected to criticism. Gorham,[8] in 1921, first showed that there were marked differences in the acid content of samples of gastric juice obtained from different parts of the stomach, and questioned whether this should not make the clinical interpretation of the results doubtful. Considerable literature, for the most part confirmatory of his results, has appeared since his publication, and although Rehfuss [9] has called attention to the fact that the method

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* From the Clifton Springs Sanitarium and Clinic.

* A preliminary report of a part of this work was read before the American Society of Gastro-Enterology, May 6, 1924.

1. Hasselbalch, K. A.: Neutralitätsregulation und Reizbarkeit des Atemzentrums in ihren Wirkungen auf die Kohlensäurespannung des Blutes, Biochem. Ztschr. **46**:403, 1912; Ammoniak als physiologischer Neutralitätsregulator, Biochem. Ztschr **74**:18, 1916.

2. Leathes, J. B.: Renal Efficiency Tests in Nephritis and the Reaction of the Urine, Brit. M. J. **2**:165 (Aug. 9) 1919.

3. Campbell, J. A.: Ammonia Excretion, Amino-Acid Excretion, and the Alkaline Tide in Singapore, Biochem. J. **14**:603, 1920.

4. Fiske, C. H.: Observations on the "Alkaline Tide" After Meals, J. Biol. Chem. **49**:163 (Nov.) 1921.

5. Hubbard, R. S., and Munford, S. A.: The Excretion of Acid and Ammonia, J. Biol. Chem. **54**:465 (Oct.) 1922.

6. Wilson, D. W.: Neutrality Regulation in the Body, Physiol. Rev. **3**:295 (July) 1923.

7. Rehfuss, M. E.; Bergeim, O., and Hawk, P. B.: Gastro-Intestinal Studies, II, The Fractional Study of Gastric Digestion with a Description of Normal and Pathologic Curves, J. A. M. A. **63**:909 (Sept. 12) 1914.

8. Gorham, F. D.: Variations of Acid Concentration in Different Parts of the Gastric Chyme and Its Relation to Clinical Methods of Gastric Analysis, Arch. Int. Med. **27**:434 (April) 1921.

9. Rehfuss, M. E.: Diagnosis of Gastric Disease, Ann. Clin. Med. **2**:55 (July) 1923.

has been used with general success in clinical work, and that this proves its value, still the bulk of the evidence tends to show that the results in any given case may be open to considerable suspicion.[10] It has seemed worth while to try to find some method for the study of gastric secretion by which gastric analyses in doubtful cases might be confirmed. If a method can be found which will agree, even approximately, with the fractional analysis, it should be useful, not only for this purpose, but also for getting information in cases in which gastric analyses cannot be obtained. With this end in view, a study of the alkaline tide in urine was undertaken.

In an earlier paper from this clinic,[11] it was found that the alkaline tides showed variations after meals containing different kinds of foodstuffs similar to those which can be demonstrated in the acidity of the gastric juice, and that in seven cases without hydrochloric acid in the stomach the tide was either absent or markedly decreased. These facts seemed to warrant further study of the method with a view of applying it as an aid in diagnosis. The present paper has been devoted to collecting data on patients with and without acid in the gastric juice, for it is on material of this kind that clinical applications of the test must be based.

A study was made of patients on whom the results of gastric analyses by the method of Rehfuss, Bergeim and Hawk[7] were available. No attempt was made to select patients, except that more pains were taken to secure urines from those in whom an achlorhydria or a very marked hypochlorhydria was found than from others, for results previously obtained[11] made it seem probable that the method might serve to pick out cases of this kind, but that it would not be delicate enough to differentiate cases with hyperchlorhydria from others. Since it was intended to apply the results to the study of clinical problems, it seemed best to carry out the tests in as nearly a routine manner as was possible. No attempt was made to secure duplicate determinations, for it is more important to know what reliance can be placed on the result of a single test than to know how good agreement can be shown under especially favorable conditions. Furthermore, it did not seem proper to repeat determinations which were probably open to suspicion, when it was not possible to repeat all. The gastric and urine tests were not carried out simultaneously, because the test was intended to be used in some cases in which gastric studies could not be obtained, and it is by no means improbable that the removal of part of the stomach contents affects the

10. Friedenwald, J. G.; Gantt, N. H., and Morrison, T. H.: Studies in Fractional Analysis, Ann. Clin. Med. **2**:292 (March) 1924.

11. Hubbard, R. S.; Munford, S. A., and Allen, E. G.: Gastric Secretion and the "Alkaline Tide" in Urine, Am. J. Physiol. **68**:207 (April) 1924.

rate of reabsorption of acid in the intestine and its subsequent excretion in the urine.

Since it has been shown that the foods eaten in the meal influence the form of the alkaline tide, it is necessary to select a standard breakfast. The one used consisted of two slices of toast, an egg, a pat of butter, a glass of milk and a glass of water. Nothing else was taken during the test, for it has been shown that a secretion of acid is brought about simply by drinking water.[12] This breakfast was the one called the "standard" in the previous work. It caused the development of a less marked tide than did those high in protein, and of a more marked one than did breakfasts which consisted almost entirely of carbohydrate. Each patient began the test at 7 o'clock in the morning by emptying the bladder. Hourly specimens were then collected until 12 or 1 o'clock. Breakfast was given from 8:15 to 8:45. There were available for study a specimen collected before breakfast, one which corresponded to the

TABLE 1.—*Average Values*

Studied	Normal *pH* 7.0	Hydrochloric Acid Present		Hydrochloric Acid Absent		Hydrochloric Acid Low *pH* 7.0
		All	*pH* 7.0	All	*pH* 7.0	
Number of determinations	8	45	35	18	16	6
Number of patients	3	45	35	18	16	6
Number of women	0	33	25	12	10	4
Time	*pH*	*pH*	*pH*	*pH*	*pH*	*pH*
1 hour before meal	5.7	6.4	6.0	6.5	6.2	6.4
1 hour at meal time	6.0	6.5	6.1	6.3	6.2	5.5
1 hour after meal	6.7	6.3	6.0	5.9	5.7	5.4
2 hours after meal	6.9	6.8	6.5	6.0	5.8	5.6
3 hours after meal	6.4	6.8	6.6	5.9	5.7	5.4
4 hours after meal	5.7	6.0	5.5	5.8	5.7	5.4

time at which the meal was eaten, and three or four obtained later. The hydrogen ion concentration of each was determined, as soon as possible after it was obtained, by a colorimetric method approximately the same as that described by Marshall,[13] with standards prepared from a buffer solution described by Acree and his co-workers.[14] Specimens were not collected directly in narrow cylinders, as recommended by Marshall; each was collected in the usual way and sent to the laboratory in a quart jar under toluene.

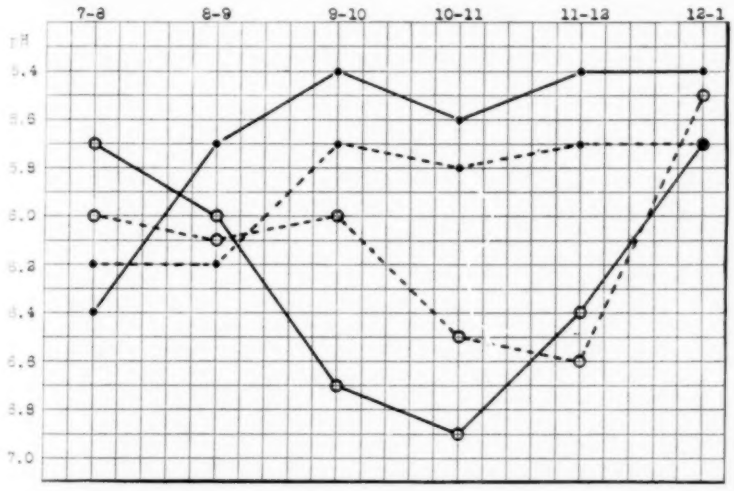
Table 1 shows the averages of all the results obtained. The normal subjects were three men laboratory workers in whose gastric contents

12. Bergeim, O.; Rehfuss, M. E., and Hawk, P. B.: Gastro-Intestinal Studies, III (Studies of Water Drinking, XXI), Direct Demonstration of the Stimulatory Power of Water in the Human Stomach, J. Biol. Chem. **19**:345, 1914.

13. Marshall, E. K., Jr.: The Effect of Loss of Carbon Dioxid on the Hydrogen Ion Concentration of Urine, J. Biol. Chem. **51**:3 (March) 1922.

14. Acree, S. F.; Mellon, R. R.; Avery, P. M., and Slagel, E. A.: A Single Stable Buffer Solution, J. Infect. Dis. **29**:7 (July) 1921.

hydrochloric acid had been demonstrated, and the others were patients from the clinic. Four of the determinations on the normal subjects were included in an article previously published.[11] It has seemed best, since Marshall [12] has shown that the results of hydrogen ion determinations on urine specimens which are alkaline are open to question, and since a considerable number of the subjects excreted urines which were alkaline or nearly alkaline throughout the test, to show not only the results from all cases but also those from cases in which the average p_H was less than 7.0. The table also includes a few experiments on subjects with very little acid in the gastric juice.



A (solid line, hollow dot), normal, eight determinations, three subjects; *B* (broken line, hollow dot), hydrochloric acid present, thirty-five determinations; *C* (broken line, solid dot), hydrochloric acid absent, sixteen determinations; *D* (solid line, solid dot), hydrochloric acid low, six determinations.

The results from subjects who did not excrete a very alkaline urine are given in the accompanying chart. The normal controls and patients in whose gastric juice acid was found showed typical alkaline tides; that is, the specimens collected in the middle of the morning were more alkaline than were those collected before or during the meal, and the reaction of the last specimen was more acid than were those of specimens collected earlier. No such tides were shown by the average figures from patients with achlorhydria or with very little acid in the stomach. These averages conform with the theory that the secretion of the gastric juice is the cause of the alkaline tide, as do results of similar alveolar air

studies by Bennett and Dodds.[15] They suggest that such urine studies may be of use in distinguishing cases with little or no acid in the gastric juice from those in which more acid is secreted.

In Table 2, detailed data of all patients secreting little or no hydrochloric acid are given. Only those cases have been included in which the amount of acid was so small, or the length of time when the acid was present was so short, that it was practically impossible that the secretion and reabsorption of it could have had any effect on the excretion of acid in the urine. In one of these six cases, a definite tide was present, but in the others there was none found, as would be expected from the gastric analyses. The percentage of cases in which the two tests agreed is the same as that found in the series as a whole, as will

TABLE 2.—*Results of Studies on Patients with Very Little Hydrochloric Acid*

RESULTS OF GASTRIC ANALYSES

Time	C.c. Tenth Normal Hydrochloric Acid in 100 C.c. Gastric Contents					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Residuum	0	0	0	0	6	5
30 minutes after meal	2.5	0	0	0	0	21
45 minutes after meal	10	0	0	0	0	11
1 hour after meal	0.5	0	0	10	0	0
1 hour 15 minutes after meal	0	3	7	26	0	..
1 hour 45 minutes after meal	0	0	0	0	0	..
2 hours 15 minutes after meal	0	..	0	0	8	..
2 hours 45 minutes after meal	..	..	..	..	0	..

ALKALINE TIDE STUDIES

Time	Hydrogen Ion Concentration of Urine Specimens					
	*p*H	*p*H	*p*H	*p*H	*p*H	*p*H
Before meal	6.8	5.6	7.0	5.7	7.0	6.5
At meal time	4.9	5.3	5.8	5.6	7.7	5.9
1 hour after meal	4.9	5.3	5.2	5.5	5.3	6.3
2 hours after meal	4.9	5.4	6.8	5.0	5.3	6.3
3 hours after meal	5.0	5.2	6.5	4.9	5.0	5.7
4 hours after meal	...	5.4	6.5	4.8	4.8	...

be shown here. The table shows that the absence of a tide is not diagnostic of a condition of achlorhydria, but it does confirm the impression that the gastric secretion is the cause of the alkaline tide.

The eight determinations on three normal subjects are given in Table 3. There were rather marked differences in the curves obtained from the same subject at different times, but the general form of each was similar to that of the average of the normal values. In the experiment in which the reaction of the first specimen was least acid, that on Case 1 in Table 3, July 10, although the differences in reaction between it and subsequent specimens were diminished, the general form of the curve resembled the others. It seems to the authors that such a find-

15. Bennett, T. I., and Dodds, E. C.: The Gastric and Respiratory Response to Meals, Brit. J. Exper. Path. **2**:58 (April) 1921.

ing should not be unexpected when the acidity of the first specimen is low. The fact that other studies on this case showed unmistakable tides suggests that, if the reaction of the first specimen in a test is not very acid, it may be worth while to repeat the test to see whether results which are more easily interpreted can be obtained.

If the results are to be used in differentiating cases with little or no hydrochloric acid from those in which acid is present, it is desirable that a definition of what changes in reaction constitute a tide shall be given. It has not been found possible to do this in an entirely satisfactory manner. Two factors must be considered in judging each case. One is the difference in the reactions of different specimens, and the other is the relationship which the reactions of different specimens bear to each other. Sometimes the differences in reaction are small, but the relationship between the values shows that a tide is present. A good illustration of this is the experiment on Case 1, July 10, recorded in Table 3. Sometimes there may be a great difference between the

TABLE 3.—*Alkaline Tide Determinations on Normal Subjects*

Time	Case 1				Case 2		Case 3	
	7/6/23	7/10/23	7/12/23	4/16/24	6/27/23	7/5/23	12/21/23	1/17/24
	p_H	p_H	p_H	p_H	p_H	p_H	p_H	p_H
1 hour before meal	5.4	6.6	5.7	5.6	5.5	5.5	5.9	5.7
1 hour at meal time	5.6	6.9	5.8	5.7	6.2	5.9	6.8	6.1
1 hour after meal	6.2	6.9	6.5	6.9	7.4	6.9	6.9	6.3
2 hours after meal	6.0	7.2	6.7	6.6	7.4	6.9	7.1	7.0
3 hours after meal	5.8	6.5	6.6	5.7	7.0	6.7	5.9	6.8
4 hours after meal	5.8	6.0	5.7	...	6.3	6.4	5.4	6.1

reactions of two specimens, and yet a study of the curve as a whole shows almost certainly that no tide is present. An example of such a result is shown in the second case in Table 4. In general, each test must be judged more or less on its own merits, and, if doubt is entertained about the meaning of the results, a duplicate study should be sought. In spite of these objections, we have formulated a definition as a basis for discussing the results. This definition, with some of the reasons which have influenced us in using it, is given below.

It has been shown, by Leathes,[2] by Collip and Backus[16] and by Grant and Goldman,[17] that a marked increase in the rate of respiration causes the excretion of an alkaline urine. Care was taken to prevent the occurrence of errors from this source, but as the effect of moderate changes of the respiratory rate cannot be determined, it has seemed

16. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnea on the Carbon Dioxid Combining Power of the Plasma, the Carbon Dioxid Tension of the Alveolar Air and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, Am. J. Physiol. **51**:568 (April) 1920.

17. Grant, S. B., and Goldman, A.: A Study of Forced Respiration; Experimental Production of Tetany, Am. J. Physiol. **52**:209 (June) 1920.

best not to accept small changes in reaction shown by one specimen as indicating the presence of a tide. Another difficulty arises from the form of the curves observed in a number of instances. In the normal subjects, the reactions of the second, third, fourth and fifth specimens were more alkaline than was that of the first one. In many studies on patients, the findings were similar, but in some, the curves were like that shown by Case 6 in Table 2. There was a low degree of acidity in the specimen obtained before breakfast, a more acid reaction in the one collected at breakfast time, and a definite tide later, with values very little, if any, more alkaline than were those of the first specimen. It is possible that the secretion of acid by the stomach is responsible for this, for the presence of hydrochloric acid in the fasting contents, lower acid concentrations during the hour following the meal, and more acid

TABLE 4.—*Cases with Achlorhydria Which Showed an Alkaline Tide*

RESULTS OF GASTRIC ANALYSES

Time	C.c. Tenth Normal Total Acid in 100 C.c. Case 1	Case 2	Case 3
Residuum	10	4	4
30 minutes after meal	8	3	6
45 minutes after meal	11	5	7
1 hour after meal	15	8	7
1 hour 15 minutes after meal	16	15	9
1 hour 45 minutes after meal	13	18	6
2 hours 15 minutes after meal	13	14	..

ALKALINE TIDE STUDIES

Time	Hydrogen Ion Concentrations Case 1	Case 2	Case 3
	pH	*pH*	*pH*
Before meal	6.0	8.4	5.6
At meal time	6.6	7.9	6.4
1 hour after meal	5.8	5.4	5.6
2 hours after meal	6.0	7.1	6.5
3 hours after meal	6.9	5.7	6.6
4 hours after meal	7.0	4.9	6.7

values later were not infrequent findings; the gastric curve of Case 6 in Table 5 may serve as an example of such determinations. Leathes,[2] however, has claimed that there is a retention of carbon dioxid during the night and a loss of that compound immediately after rising because of the increased activity of the subject and the consequent increase in the rate of ventilation. This increased rate of ventilation causes a tendency toward the secretion of an alkaline urine, just as did the experiments on hyperpnea already mentioned. It seems possible that such a process of readjustment as this might account for the low acidity of the first specimen with a subsequent excretion of a more strongly acid urine sometimes observed. Whatever is the cause of these variations in the first two hours of the test, the fact that they occur makes it seem inadvisable to consider the reaction of the specimen collected before breakfast as the only one with which those of later specimens is compared.

The criteria finally adopted for determining whether or not there was a tide in a given case were as follows: If any specimen was more alkaline than one collected earlier in the test by 1 p_H or more, or if any two were more alkaline by 0.5 p_H, we considered that a tide was present. The application of this can be seen in Table 4. The fourth specimen in the second case was more alkaline than the third by 1.7 p_H, and in the third case the fourth and fifth specimens were more alkaline than were the first and third by more than 0.5 p_H. Therefore, we consider that a tide was present in both of these cases.

When the cases were judged by the test proposed, it was found that the presence and absence of a tide agreed with the results of the frac-

TABLE 5.—*Cases with Hydrochloric Acid in the Gastric Juice Which Showed No Alkaline Tide*

RESULTS OF GASTRIC ANALYSES

Time	C.c. Tenth Normal Hydrochloric Acid in 100 C.c. Gastric Contents						
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Residuum	0	20	19	25	0	19	0
30 minutes after meal	0	10	21	62	0	23	33
45 minutes after meal	16	25	38	45	22	0	48
1 hour after meal	26	31	40	39	44	0	49
1 hour 15 minutes after meal	20	35	42	52	22	7	62
1 hour 45 minutes after meal	30	35	50	45	..	30	16
2 hours 15 minutes after meal	..	24	..	..	..	16	..
2 hours 45 minutes after meal	..	..	..	..	..	25	..
3 hours 15 minutes after meal	..	..	..	..	..	30	..

ALKALINE TIDE STUDIES

Time	Hydrogen Ion Concentration of Urine Specimens						
	p_H	p_H	p_H	p_H	p_H	p_H	p_H
Before meal	5.9	5.2	5.7	6.1	6.7	5.0	5.3
At meal time	5.8	5.0	5.5	6.2	6.2	5.3	5.8
1 hour after meal	5.1	5.2	5.3	5.7	5.7	5.2	5.5
2 hours after meal	5.2	5.1	5.6	5.8	5.8	5.5	5.3
3 hours after meal	5.8	4.9	5.4	6.3	5.6	5.3	5.2
4 hours after meal	5.4	4.9	5.5	5.9	5.2	...	5.3

tional gastric analyses in 80 per cent. of them. Table 4 gives detailed results on the gastric and tide tests in the cases of achlorhydria which showed a tide, and Table 5 gives similar data on the cases when hydrochloric acid was present but which failed to show one. In some of the cases included, the general impression given by the findings does not agree with the decision based on an arbitrary application of our standard; if such results had been met with in tests carried out for diagnostic purposes, we should have tried to secure another test as a check on them. Another factor which may have produced discrepancies is the variations in the results of the determinations which occur from day to day. It has been shown in the present paper that this is true of the alkaline tide tests, and the same thing has been shown to apply to gastric analyses

also.[18] Repeated determinations of gastric analyses and urine studies would have helped in eliminating such sources of error, but, as already stated, it did not seem best to make them. It has seemed better to accept a discrepancy of 20 per cent. between the results of the two tests rather than to press explanations of the failures.

Another factor which may sometimes affect the results remains to be discussed. It is not certain what effect damage to the kidneys may have on the alkaline tide.[2] The literature dealing with the effect of nephritis on the reaction of the urine has recently been reviewed by Rabinowitch[19] and by Stieglitz.[20] It has been shown by them, and by the authors whom they cited, that nephritis does influence the excretion of acid. It does not seem unlikely that the differences between the reactions of different specimens would also be influenced by kidney damage. It seems probable to the authors that the effect would be to decrease these differences. No direct evidence on this point was obtained, for no patients with severe nephritis were studied. We have found normal rates of the excretion of phenolsulphonephthalein in some of the cases of achlorhydria in which a tide was absent, and have occasionally observed considerable differences in the reactions of different specimens of urine from nephritic patients. In spite of these observations, a possible effect of kidney disease on the alkaline tide should be kept in mind in interpreting results.

Variations in the reaction of the urine have been compared with the results of fractional gastric analyses. The average values showed that definite changes in the reaction of the urine, commonly known as the alkaline tide, were present in specimens from patients who secreted more than minimal amounts of hydrochloric acid in the gastric juice, but that no such changes were found when the stomach contents contained little or no acid. A method for determining whether or not a tide is present in a given case has been proposed, and it has been shown that, as judged by it, the presence or absence of a tide agreed with the results of fractional gastric analysis in about 80 per cent. of the cases studied. The presence or absence of the tide cannot be taken as the final proof of the presence or absence of hydrochloric acid in the stomach, because the results of the two analyses do not agree perfectly, because an absence of the tide can be demonstrated in cases in which acid is present in greatly reduced amounts, and because the urine acidity is influenced by

18. Bell, J. R., and MacAdam, W.: The Variations in Gastric Secretion of the Normal Individual, Am. J. M. Sc. **167**:520 (April) 1924. Friedenwald, Gantt and Morrison (Footnote 10).

19. Rabinowitch, I. M.: The Origin of Urinary Ammonia, second paper, Arch. Int. Med. **33**:394 (March) 1924.

20. Stieglitz, E. J.: Histologic Hydrogen Ion Studies of the Kidney, Arch. Int. Med. **33**:483 (April) 1924.

some factors, such as changes in the respiratory rate and, possibly, kidney damage, which are not connected with the gastric secretion. The method should prove useful in studying gastric cases on which direct analyses cannot be obtained, and in checking results showing low concentrations of acid in the gastric juice, for the agreement between the two methods is good if not perfect, and the factors which influence the reaction of the urine are very different from those which sometimes render the values obtained in fractional gastric analysis uncertain.

SIMULTANEOUS DETERMINATIONS OF GASTRIC ACIDITY AND THE ALKALINE TIDE IN URINE*

ROGER S. HUBBARD, PH.D., AND ELLERY G. ALLEN, A.B.
CLIFTON SPRINGS, N. Y.

In the preceding paper, it has been shown that an alkaline tide can be demonstrated in most cases in which hydrochloric acid is secreted by the stomach, but is not present in cases of achlorhydria or in subjects who secrete very little acid. The present paper is a brief report of a few experiments made to determine how much acid the stomach must secrete to cause the changes in the urine.

In the experiments reported in the preceding article, gastric analyses and alkaline tide determinations were not made simultaneously. There are obvious objections to comparing directly results so obtained. In some cases, the gastric curves found on the same subject resemble each other closely;[1] in others, this is not true.[2] In some instances, variations in the acidity in different parts of the stomach[3] may account for the findings, for the tube may rest in different parts of the organ, but even when the gastric juice is thoroughly mixed before the specimens are taken marked variations in the curves are sometimes, though rarely, found.[4] It seems probable that nausea and psychic states, such as fear and rage, which have an influence on the gastric secretion of man,[5] may sometimes cause the discrepancies.

In carrying out simultaneous determinations, other difficulties were encountered which rendered the interpretation of the results uncertain. It has been shown in an earlier article[6] that tides are sometimes practically absent after meals high in carbohydrate; to study these changes

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* From the Clifton Springs Sanitarium and Clinic.

1. Bennett, T. I., and Ryle, J. A.: Studies on Gastric Secretion, V, A Study of Normal Gastric Secretion Based on the Investigation of One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, Guy's Hosp. Rep. **71**:286 (July) 1921.

2. Bell, J. R., and MacAdam, W.: The Variations in Gastric Secretion of the Normal Individual, Am. J. M. Sc. **167**:520 (April) 1924.

3. Gorham, F. D.: Variations of Acid Concentration in Different Parts of the Gastric Chyme and Its Relation to Clinical Methods of Gastric Analysis, Arch. Int. Med. **27**:434 (April) 1921.

4. Friedenwald, J. G.; Gantt, N. H., and Morrison, T. H.: Studies in Fractional Analysis, Ann. Clin. Med. **2**:292 (March) 1924.

5. Ryle, G. A.: Studies in Gastric Secretion, IV, Some Individual Experiments with the Gastric Tube, Guy's Hosp. Rep. **71**:158 (April) 1921. Bennett, T. I., and Venables, J. F.: The Effect of the Emotions on Gastric Secretion and Motility in the Human Being, Brit. M. J. **2**:662 (Oct. 30) 1920.

6. Hubbard, R. S.; Munford, S. A., and Allen, E. G.: Gastric Secretion and the "Alkaline Tide" in Urine, Am. J. Physiol. **68**:207 (April) 1924.

in the reaction of urine, it is therefore necessary to use meals containing various foodstuffs. Such meals often give curves, when fractional analyses are carried out, which are difficult to interpret. If an attempt is made to find out how much acid is needed to cause a change in the reaction of the urine, it is necessary to know not only the concentration of acid in the gastric juice but also how much of it is formed in a given time. This cannot be determined without removing the entire gastric contents at frequent intervals. Such a procedure would make a study of the changes in the reaction of the urine meaningless, for the acid would not be reabsorbed in the intestinal tract, and no tide which even approximated those normally present could be obtained. It is even uncertain whether tides found when small specimens are withdrawn can properly

TABLE 1.—*Breakfasts*

Name	Sign	Foodstuffs	Foods	Grams
Gastric test meal.....	T	2 slices of bread soaked in water.....	Carbohydrate	33
			Protein.....	6
High protein.....	P	100 gm. cottage cheese, 105 gm. steak, albumin of 5 boiled eggs, 228 c.c. of water	Carbohydrate	4
			Protein.....	63
			Fat.....	13
Standard.....	S	60 gm. toast, 13 gm. butter, 50 gm. egg, 200 c.c. milk, 200 c.c. water	Carbohydrate	42
			Protein.....	19
			Fat.....	26
High carbohydrate 1....	C 1	110 gm. pitted dates, 25 gm. shredded wheat, 7 gm. sugar, 356 c.c. water	Carbohydrate	106
			Protein.....	4
			Fat.....	3
High carbohydrate 2....	C 2	88 gm. pitted dates, 25 gm. shredded wheat, 5 gm. sugar, 468 c.c. water	Carbohydrate	75
			Protein.....	3
			Fat.....	3
High carbohydrate 3....	C 3	25 gm. shredded wheat, 24 gm. sugar, 60 gm. bread, 250 c.c. water	Carbohydrate	75
			Protein.....	9
			Fat.....	1
High carbohydrate 4....	C 4	25 gm. shredded wheat, 103 gm. stewed prunes, 3 gm. sugar, 430 c.c. water	Carbohydrate	56
			Protein.....	4
			Fat.....	0.5

be considered normal. In spite of these objections to the interpretation of results, it has seemed worth while to carry through a few experiments to show approximately what concentration of acid corresponds with the presence of a tide.

In these experiments, a Rehfuss tube was passed, and a specimen of gastric residuum removed. Different meals were fed, and specimens withdrawn at intervals of half an hour throughout the experiment.[7] The alkaline tide was determined by the method described in the preceding article. The meals used, with the abbreviations by which they have been designated in the discussion, are given in Table 1.

7. Rehfuss, M. E.: A New Method of Gastric Testing, with a Description of a Method for the Fractional Testing of the Gastric Juice, Am. J. M. Sc. **147**:848, 1914. Rehfuss, M. E.; Bergeim, O., and Hawk, P. B.: Gastro-Intestinal Studies, II, The Fractional Study of the Gastric Juice with a Description of Normal and Pathologic Curves, J. A. M. A. **63**:909, 1914.

In Table 2, all the gastric analyses obtained on one of us, E. G. A., a normal man doing light laboratory work, are given. After the test meal, the relationship between the hydrochloric acid and total acid was normal, but when other breakfasts were fed, the total acid concentration was very high compared with the amount of hydrochloric acid present. The difference was most marked when the breakfasts contained large amounts of carbohydrate. This finding may be due to a partial neutralization of hydrochloric acid by the products of digestion, to the presence of acid products formed from the food in the course

TABLE 2.—*Gastric Analyses on Normal Subject, E. G. A., After Different Meals*

	T		S		P		C 1		C 3		C 4	
Meal Time	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.
Residuum	0	13	0	0	0	11	0	23	0	8	30	72
After												
0:20	..	..	..	..	0	53	..	..	..	..	..	..
0:30	6	18	0	42	0	80	0	88	3	21	Trace	61
1:00	20	53	3	81	Trace	55	0	110	5	31	0	80
1:30	36	54	23	87	17	91	0	71	21	50	14	69
2:00	35	51	22	91	30	68	18	78	30	54	24	68
2:30	..	..	38	93	58	102	0	36	15	34	39	64
3:00	..	..	35	95	60	127	0	12	11	26	32	48
3:30	..	..	69	91	70	130	0	7	30	46	Trace	48
4:00	..	..	56	68	60	87	..	..	6	8	..	..
4:30	..	..	0	12	41	67	..	..	..	..	..	..
5:00	..	..	..	..	35	62	..	..	..	..	..	..

TABLE 3.—*Gastric Analyses on Patient with Hypochlorhydria*

	T		S	
Meal	Hydrochloric Acid, C.c.	Total, C.c.	Hydrochloric Acid, C.c.	Total, C.c.
Residuum	None obtained		0.0	5.0
After meal 0:30	0.0	4.0	....	....
0:45	0.0	6.0	....	....
1:00	0.0	7.0	0.0	34.0
1:15	2.0	20.0	....	....
1:30	....	....	0.0	27.0
1:45	12.0	32.0	....	....
2:00	....	....	0.0	23.0
2:15	13.0	32.0	....	....
2:30	....	....	0.0	30.0
2:45	Trace	15.0	....	....
3:00	....	....	0.0	40.0
3:30	....	....	0.0	28.0

of digestion, or to both causes. In Table 3, results on another subject are given which make it seem probable that these increases in total acid are due in part at least to the neutralization of hydrochloric acid, for an achlorhydria was found when the standard breakfast was fed, while after the gastric test meal hydrochloric acid was present, although only in small amounts. If this explanation is correct, it is not possible to determine in a satisfactory manner the relationship between the concentration of acid in the gastric secretion and the alkaline tide, for a secretion of hydrochloric acid by the stomach, whether it is or is not neutralized, must cause the changes in the blood which produce the alkaline tide.[8]

8. Bennett, T. I., and Dodds, E. C.: The Gastric and Respiratory Response to Meals, Brit. J. Exper. Path. **2**:58 (April) 1921.

TABLE 4.—*Results on Subject, E. G. A.*

Fractional Gastric Analysis				Alkaline Tide	
		Hydrochloric Acid	Total		
	Time,	Tenth Normal per 100 C.c		Hour,	Reaction.
Meal	A. M.	C.c.	C.c.	A. M.	p_H
T	.....	....	...	7:20- 8:20	5.6
	9:20 (residuum).....	0.0	13.0	8:20- 9:20	5.6
	10:05.....	6.0	18.0		
				9:20-10:20	5.8
	10:50.....	20.0	53.0		
	11:10.....	36.0	54.0		
				10:20-11:20	5.7
	11:45.....	35.0	51.0		
				11:20-12:20	5.8
S	.....	....	...	7:00- 8:00	5.7
	8:35 (residuum).....	0.0	6.0		
				8:00- 9:00	5.8
	9:05.....	0.0	42.0		
	9:35.....	3.0	81.0		
				9:00-10:00	6.4
	10:05.....	23.0	87.0		
	10:35.....	22.0	91.0		
				10:00-11:00	6.5
	11:05.....	38.0	93.0		
	11:35.....	55.0	95.0		
				11:00-12:00	6.0
	12:05.....	69.0	91.0		
	12:35.....	56.0	68.0		
				12:00- 1:00	5.6
P	.....	....	....	7:30- 8:30	5.7
	8:50 (residuum).....	0.0	11.0		
	9:10.....	0.0	53.0		
	9:30.....	0.0	80.0		
				8:30- 9:30	5.7
	9:50.....	Trace	55.0		
	10:20.....	17.0	91.0		
				9:30-10:30	6.6
	10:50.....	30.0	68.0		
	11:20.....	58.0	102.0		
				10:30-11:30	7.0
	11:50.....	60.0	127.0		
	12:20.....	70.0	130.0		
				11:30-12:30	6.5
	12:50.....	60.0	87.0		
	1:20.....	41.0	67.0		
				12:30- 1:30	5.4
	1:50.....	35.0	62.0		
				1:30- 2:00	5.0
C 4	.....	....	....	7:45- 8:20	5.5
	8:40 (residuum).....	30.0	72.0		
	9:10.....	Trace	61.0		
				8:20- 9:20	5.6
	9:45.....	0.0	80.0		
	10:10.....	14.0	69.0		
				9:20-10:20	5.8
	10:40.....	24.0	68.0		
	11:10.....	39.0	64.0		
				10:20-11:20	6.5
	11:40.....	32.0	48.0		
	12:10.....	Trace	48.0		
				11:20-12:20	5.6
C 3	.....	....	....	7:00- 8:10	5.7
	8:25 (residuum).....	0.0	8.0		
				8:10- 9:10	5.8
	9:15.....	3.0	21.0		
	9:45.....	5.0	31.0		
				9:10-10:10	6.4
	10:15.....	21.0	50.0		
	10:45.....	30.0	54.0		
				10:10-11:10	6.5
	11:15.....	15.0	34.0		
	11:45.....	11.0	26.0		
				11:10-12:10	6.0
	12:15.....	30.0	46.0		
	12:45.....	0.0	8.0		
				12:10- 1:10	5.6

TABLE 4.—*Results on Subject, E. G. A.—(Continued)*

	Fractional Gastric Analysis			Alkaline Tide	
Meal	Time, A. M.	Hydrochloric Acid Tenth Normal per 100 C.c. C.c.	Total C.c.	Hour, A. M.	Reaction, P_H
C 1	.....	....	....	7:30- 8:30	5.4
	8:40 (residuum).....	0.0	23.0		
	9:10.....	0.0	88.0	8:30- 9:30	5.4
	9:40.....	0.0	110.0		
	10:10.....	0.0	71.0	9:30-10:30	5.3
	10:40.....	18.0	78.0		
	11:10.....	0.0	36.0	10:30-11:30	5.0
	11:40.....	0.0	12.0		
	12:05.....	0.0	7.0	11:30-12:30	5.2

The meals were fed immediately after the residual specimens were obtained.

In Table 4, the results of simultaneous studies on the urine and gastric contents of subject E. G. A. are given. In the alkaline tides from him, when the tube was not in the stomach, as have been previously described,[8] it was found that the intensity of the tide varied with the meals fed in much the same manner as did the secretion of hydrochloric acid after similar meals reported by others.[9] The results reported here conform to the figures previously obtained. The meal highest in protein caused the highest secretion of acid in the gastric juice and the most marked tide found in any of the experiments. A similar meal caused the most marked tide in the previous study. The meal highest in carbohydrate was followed by a secretion of very small amounts of acid and no tide; in the previous study, no tide followed the ingestion of the meal highest in carbohydrate used. Concentrations of acid and intensities of tides found after other meals were intermediate, and varied approximately as the concentrations of protein in the meals; in the results presented in the other paper, the depth of the tide after the standard breakfast was intermediate between those which followed meals higher in protein and in carbohydrate. These results furnish strong confirmation of the theory that the secretion of hydrochloric acid determines the presence and intensity of the alkaline tide.

It is difficult to decide from the results the amount of hydrochloric acid which must be secreted to produce a tide. A concentration of 35 c.c. of tenth normal hydrochloric acid and 54 c.c. of tenth normal total acid after the gastric test meal, Experiment T, was not accompanied by a tide, while 24 c.c. of hydrochloric acid and 68 c.c. of total acid (Experiment C 4) and 21 c.c. of hydrochloric acid and 50 c.c. of total acid (Experiment C 3) did cause tides. We feel that there are enough unavoidable factors, such as variations in the amount of gastric juice

9. Rehfuss, M. E., and Hawk, P. B.: A Consideration of the Gastric Test Meal from Experimental Data, J. A. M. A. **75**:449 (Aug. 14) 1920.

secreted, variations in concentration of hydrochloric acid in different parts of the stomach, and partial neutralization of hydrochloric acid secreted, to account for these discrepancies.

In Table 5, data obtained in a somewhat different way are reported. The same subject took the meals indicated. Tides developed, and half way through each experiment a tube was swallowed and a sample of gastric juice obtained. Thirty-five cubic centimeters of hydrochloric acid and 47 c.c. of total acid in one experiment, and 44 c.c. of hydrochloric acid and 106 c.c. of total acid in the other caused tides. In the second result, the large amounts of total acid found make it seem probable that a part of the hydrochloric acid produced by the stomach had been neutralized by products of digestion, and therefore it does not

TABLE 5.—*Single Specimen Gastric Analysis and Tides in E. G. A.*

	Single Specimen Gastric Study			Alkaline Tide	
Meal	Time. A. M.	Hydrochloric Acid Tenth Normal per 100 C.c. C.c.	Total C.c.	Hour. A. M.	Reaction. *pu*
C 2	.....	....	....	7:32- 8:37	5.6
				8:37- 9:37	5.6
				9:37-10:37	6.4
	10:43.....	35.0	47.0		
				10:37-11:37	6.7
				11:37-12:37	5.6
S	.....	....	....	7:20- 8:30	5.6
				8:30- 9.30	5.7
				9:30-10:30	6.9
	10:45.....	44.0	106.0		
				10:30-11:30	6.6
				11:30-12:30	5.7

The tube was swallowed just before the gastric specimen was obtained. The meals, as indicated, were taken about half an hour after the first urine specimen was voided.

seem unreasonable that a tide should be found, but the figures in the first experiment are almost identical with those found after the gastric test meal (Experiment T, Table 4) when no tide developed. We are inclined to attribute the discrepancy to differences in the total amount of gastric juice secreted, although variations in the acidity of different parts of the stomach cannot be excluded as a cause.

In Table 6, results on three other subjects who took the standard breakfast are given. In Case 1, large amounts of acid were present in the gastric juice, and a marked tide developed; Case 2 showed no hydrochloric acid and but little total acid in the gastric juice, and an absence of a tide in the urine specimens; Case 3 also showed an achlorhydria, but it was associated with somewhat larger amounts of total acid and a well marked alkaline tide. A gastric analysis after the usual test meal was carried out on the patient, and some hydrochloric acid found, as shown in Table 3. Qualitatively, these results agree well with the theory of an association between the secretion of the gastric juice and the occurrence of the alkaline tide, but quantitatively, they are

hard to interpret, for a tide developed in Case 3 when the stomach contained no hydrochloric and only 40 c.c. of tenth normal total acid in 100 c.c. In this last case, some hydrochloric acid was probably neutralized, for gastric analysis after the usual test meal showed hydrochloric acid present, but this does not account adequately for the discrepancy between the gastric and urine findings. It seems to us that the samples drawn, in this case, do not accurately represent conditions in the stomach as a whole.

The experiments described above furnish throughout strong evidence in favor of the theory that the secretion of acid by the stomach causes the alkaline tide in urine, but owing to difficulties in determining the actual

TABLE 6.—*Results on Three Patients*

	Fractional Gastric Analysis			Alkaline Tide	
Number	Time, A. M.	Hydrochloric Acid Tenth Normal per 100 C.c. C.c.	Total C.c.	Hour, A. M.	Reaction, p_H
1	.....	....	....	7:00- 8:00	5.8
	8:30 (residuum).....	0.0	15.0		
	9:30.....	0.0	37.5		
	10:00.....	0.0	61.0		
	10:30.....	6.0	83.0	8:00-10:00	7.2
	11:00.....	10.0	87.0	10:00-11:00	8.0
	11:30.....	67.5	98.5		
	12:00.....	75.0	96.0	11:00-12:00	8.0
2	.....	....	....	7:00- 8:00	7.7
	8:30 (residuum).....	0.0	3.0		
				8:00- 9:00	6.9
	9:30.....	0.0	22.0		
				9:00-10:00	6.2
	10:45.....	0.0	19.0		
				10-00-11:00	6.6
	11:45.....	0.0	22.0		
				11:00-12:00	6.7
3	.....	....	....	7:00- 8:00	5.9
	8:30 (residuum).....	0.0	5.0		
				8:00- 9:00	5.9
	9:30.....	0.0	34.0		
	10:00.....	0.0	27.0	9:00-10:00	5.7
	10:30.....	0.0	23.0		
	11:00.....	0.0	30.0	10:00-11:00	6.4
	11:35.....	0.0	40.0		
	12:00.....	0.0	28.0	11:00-12:00	6.8

The standard breakfast, S, was fed to each patient between 8:30 and 9 a. m.

amount of hydrochloric acid secreted by the stomach at any given time, in deciding how much of the hydrochloric acid produced has been neutralized by products of digestion, and in making sure that the results of an analysis represent conditions in the whole stomach, they furnish only a little help in studying how much acid must be secreted by the stomach to produce a tide. It is certain that some acid may be present in the stomach without causing these changes in the urine, and in some cases such amounts as occur in normal gastric juice may be present, at least in part of the stomach, without producing these changes in the urine. When a tide is present, therefore, it seems probable that the

presence in the stomach of more hydrochloric acid than is usually secreted in hypochlorhydria must be assumed, in most cases. The patient may, nevertheless, have this condition, for the meals used in studying the tide lead to a production of higher concentrations of acid than do those used in the usual gastric tests, and it is on the response of the stomach to gastric test meals that the definitions of hypochlorhydria and hyperchlorhydria are based.

ATYPICAL CASE OF SPLENOMEGALY*

I. TREIGER, M.D.
CHICAGO

The case of splenomegaly to be reported shows such an atypical course that we feel that it will be justifiable to report it now, while the patient is yet under observation.

REPORT OF CASE

A woman, aged 60, with a negative family history, had an attack of typhoid fever, at the age of 10. At 29, during the seventh month of pregnancy, she suffered from eclampsia, with miscarriage. The next year, she had a second miscarriage, in the eighth month of gestation. For the following five years, she felt very weak, and gave birth to a delicate child. For the next six years, there was some improvement, during which time she gave birth to two healthy children. At 41, during her sixth pregnancy there was a recurrence of the weakness, with constant pain in the region of the spleen. A diagnosis of enlarged spleen was made and extirpation of the spleen advised, but it was refused by the patient. Since that time, her complaints have been the same—weakness, nervousness, palpitation of the heart, pain in the arms and legs, and pain in the abdomen, first on the left side but for the last few years on the right side, in the region of the liver. The bowels and kidneys were normal. There was no bleeding from any place.

Physical examination made in July, 1914, revealed that the spleen was enlarged and hard, extending to the umbilicus. The lymph glands were not enlarged. The liver was nonpalpable. The blood count was: erythrocytes, 3,008,000; leukocytes, 8,300. The differential count was: polymorphonuclears, 64 per cent.; small lymphocytes, 17 per cent.; large lymphocytes, 14 per cent., and transitionals, 5 per cent. Myelocytes were absent.

Examination made in August, 1915, gave the following findings: The spleen extended almost to the midline, and below the umbilicus to the crest of the left ilium; the edge was sharp, the notch palpable. It was not tender. The liver was not palpable. The Wassermann reaction was negative. Erythrocytes totaled 3,616,000 and leukocytes, 5,600; the differential count was normal; there were no abnormal cells found.

Examination in December, 1923, gave the following results: The spleen extended to the midline and reached into the pelvis. It was hard, smooth and not painful. The lymph glands were not enlarged. The liver extended down to the umbilicus, was hard, smooth and rather tender.

The last examination, in May, 1924, gave the following findings: The patient appeared poorly nourished. The skin was brown, smooth and dry. Some of the cervical, inguinal and axillar lymph glands were slightly enlarged. They were solid, freely movable, smooth and not tender. The throat and mouth were negative. The heart was normal, except for a slight, functional systolic murmur. The lungs were normal. Neither kidney was palpable. There was no jaundice, no dilated veins, and no evidence of ascites. The spleen was greatly enlarged, to the upper margin at the eighth rib, extending to the umbilicus and continuing in a downward direction, 3 inches (7.6 cm.) to the right of the midline, and

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* From the outpatient medical department, University of Illinois College of Medicine.

into the pelvis 3 inches (7.6 cm.) below the umbilicus. The notch was plainly felt in the region of the umbilicus. The surface was smooth, firm, and not tender to pressure. The spleen was movable. The upper border of the liver was at the level of the sixth rib, the lower border at the level of the umbilicus. The surface was smooth, firm and tender to pressure. The edge was sharp. The genitalia, extremities and reflexes were normal.

During the ten years that the patient has been under our observation, a number of careful blood studies have been made, showing only secondary anemia with leukopenia. The first changes occurred Oct. 15, 1923, when the blood findings were as follows: Erythrocytes, 3,584,000; hemoglobin, 55 per cent. (Sahli), and leukocytes 4,200. The differential count showed polymorphonuclears, 38 per cent.; large lymphocytes, 4 per cent.; small lymphocytes, 8 per cent.; transitionals, 7 per cent.; eosinophils, 3 per cent.; basophils, 2 per cent.; neutrophilic myelocytes, 25 per cent.; eosinophilic myelocytes, 4 per cent.; basophilic myelocytes, 2 per cent.; myeloblasts, 2 per cent., and normoblasts, 5 per cent. The red cells showed variation in size and shape, with rare polychromatophilic cells and stippling. The platelets were increased in number, and were frequently abnormally large. The numbers of leukocytes were increasing until, May 5, 1924, they reached 38,600. The white count was irregular, with periods of spontaneous remissions.

December 22, the general condition of the patient was unchanged and she was able to perform her house duties. The spleen was not more enlarged than it was in May. The blood counts constantly showed: secondary anemia; a white cell count of 25,000; myelocytes and normablasts.

COMMENT

The striking feature of this case is its long continued course. The progress of the disease can be divided into three periods: (1) splenic, (2) hepatic and (3) myeloid stage.

Enlargement of the spleen was diagnosed nineteen years ago. Since typhoid fever in childhood, the patient had felt weak and nervous. The symptoms became more pronounced after eclampsia, thirty years ago. It is possible that the spleen, enlarged during typhoid fever, never returned to its normal size, rendering it more susceptible to injury during eclampsia.

Enlargement of the liver was absent nine years ago. The blood pictures, in the splenic and hepatic stages, show only signs of anemia and leukopenia, which are common findings in diseases of the spleen, such as neoplastic growths.

The myeloid stage was initiated during October, 1923. It was characterized by definite changes in the bone marrow, manifested by typical myeloid changes in the blood.

It is well known that the spleen, liver and bone marrow are interrelated in their action. It is probable that the normal regulatory action of the spleen over the bone marrow was altered in such a manner as to cause an abnormal depression of the activity of the bone marrow without marked alteration of its character, as is evidenced in the chronic anemia and leukopenia, and by enlargement of the spleen and liver. In the

myelogenous stage there is hyperactivity of the bone marrow, giving rise to increased leukocyte count, and appearance of nucleated erythrocytes, myelocytes and blood platelets. The hyperactivity of the bone marrow may represent periods of remission when the bone marrow is able to overcome its depression of function, or may indicate that the spleen is affected to such a degree that the bone marrow is forced to increased activity, as is often seen after the removal of the spleen. It cannot yet be definitely stated whether the myelogenous stage is a remission or an indication of progression of the disease to a terminal stage. Clinical findings make the latter more probable.

The clinical course and our observation make very improbable the possibility that a chronic splenomegaly of very long duration with absolute absence of pathologic cells in blood changed now to another new disease—subleukemic myelosis (splenomyelogenous leukemia). Here the myeloid stage is only a biologic reaction of the bone marrow.

In Banti's splenomegaly, the tendency to hemorrhages, especially from the stomach and the rectum, is very prominent. The blood picture always shows secondary anemia and leukopenia. The third terminal stage of the disease shows symptoms simulating atrophic cirrhosis of the liver, ascites being the principal one.

Although a review of the literature of splenomegaly does not yield a description of a case of splenomegaly with the myelogenous stage, still it seems logical to expect such an involvement, in view of the close interdependence of the spleen and bone marrow.

The etiology of such diseases is still obscure. Infectious diseases, especially those which, like typhoid fever, seriously affect the spleen, are supposed to be predisposing. The effect of disturbances of the inner secretions is still unknown. The physiology of the correlations between the spleen and the bone marrow is not well enough established to make clear the etiology of such cases.

Since the etiology is obscure, the treatment, either medical or surgical, is not satisfactory in such cases. The patient was treated symptomatically for a long period, but without results. Roentgen-ray treatment also was not effective. Treatment has been discontinued, and the patient remains in the same condition as before.

SUMMARY

A woman, aged 60, who had had typhoid fever at the age of 10, and eclampsia at 31, nineteen years ago received a diagnosis of enlarged spleen. The present findings were a greatly enlarged spleen and liver. The blood findings were anemia and leukopenia until a few months ago.

when leukocytosis, with myeloid changes, appeared. The course of the disease was divided into the three stages, splenic, hepatic and myeloid; the first stage lasted over a period of twenty years, the second over a period of a few years, and the last has been in evidence for nine months.

The spleen, liver and bone marrow are interrelated in their function. Our case represents a pathologic correlation of these three, while usually only involvement of the spleen and liver is seen.

THE MECHANISM OF REACTION OF NON-SPECIFIC PROTEIN AGENTS IN THE TREATMENT OF DISEASE

I. THE INFLUENCE OF VARIOUS AGENTS ON TEMPERATURE AND LEUKOCYTE COUNTS IN NORMAL PERSONS AND IN RABBITS *

CHINGSON Y. LING, M.D.
PHILADELPHIA

Just what portion of a protein stimulates the thermoregulatory center in nonspecific protein therapy is still an open subject for investigation; likewise, the degree of therapeutic activity to be ascribed to fever production is a subject of speculation.

Lüke [1] believes that temperatures per se are not damaging factors in infections, for if in infectious diseases the temperature is artificially raised, the disease is seemingly favorably influenced. Antibodies that had gradually disappeared after an infection, or following immunization artificially produced, were again found in the serum after any procedure that increased the body temperature, whether by increasing the the external temperature, by influencing the thermal center of the brain or by injecting pyrogenic drugs. It tends to show that hyperthermia has a direct stimulating effect on the previously formed antibodies, causing the latter to mobilize freely and thus, in turn, to influence the disease processes.

On the other hand, Uddgren,[2] as a result of extensive studies with milk injections, was led to believe that hyperthermia alone could not be responsible for the clinical improvements observed. Working on eye diseases, she found that with sterile milk the reaction of the patients was mild but the therapeutic results were just as good as, if not better than, when market milk was used, which gave a severe febrile reaction.

The reactive temperature following a single injection of foreign protein, varying from a mere suggestion of febrile disturbance to a decided rise of from 1 to 2 degrees Fahrenheit, or even more, has been recorded.[3] Most observers seem to agree, however, that together with

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* From the Department of Bacteriology and Immunology, Graduate School of Medicine of the University of Pennsylvania.

1. Quoted from Petersen, W. F.: Protein Therapy and Nonspecific Resistance, New York, Macmillan Company, 1922, p. 90.

2. Uddgren, G.: Milchinjection in der Opthalmologie, Stockholm, 1918, quoted from Petersen, W. F.: Protein Therapy and Nonspecific Resistance, New York, Macmillan Company, 1922, p. 90.

3. Barkan, O., and Nelson, R. F.: The Active Agent in Milk Injection, J. A. M. A. **82**:190 (Jan. 19) 1924.

the desired therapeutic results following protein treatment a rise of temperature to some extent is usually expected.

Now, let us turn for a moment into nonspecific response of peripheral blood leukocytes. The fact that leukocytes do not constitute the main source from which to derive the defensive factors in immune processes has now been fairly well established. This does not deny in the least, however, the important rôle played by them as phagocytes, especially by neutrophilic polymorphonuclears and by large lymphocytes, in combating the infections.

Furthermore, leukocytes may possibly liberate endolysins, which exercise, as do the bacteriolysins, bactericidal activities in the blood.[4] They also may elaborate proteolytic and peptolytic enzymes [5] (leukoproteases) helping to digest and to eliminate any foreign proteins invading the system.

The rôle of leukocytes, in immune processes, has been extensively studied, though by no means is it an exhausted field of research. The works of Metchnikoff and his pupils on phagocytosis, those of Schattenfroh, Petterson, Hiss and others on bactericidal activities of leukocytes, and those of Petersen and others on leukocytic enzymes have well covered these fields. It will be unnecessary to enter here into these subjects which are so well known and of which the literatures are so accessible. The discussions in Kolmer's "Infection, Immunology and Biologic Therapy" give a comprehensive idea of these subjects.

With the introduction of nonspecific protein therapy, various agents, such as horse serum, milk, peptone, vaccines of various kinds, yeasts, crotalin and distilled water, have been employed. Leukocytic responses have been carefully studied by Lange,[6] Scully,[7] Gow,[8] Spangler,[9] Barkan [3] and others. The total leukocyte counts made after one single injection of protein, varying from 15,000 to 30,000, have been observed. In most cases, the reactive leukocytosis that follows is of myeloid types, that is, of neutrophilic polymorphonuclears, large mononuclears and transitional types. Eosinophils also are increased at times. The lymphatic apparatus is relatively passive.

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4. Manwaring, W. H.: The Nature of the Bactericidal Substance in Leukocytic Extract, J. Exper. Med. **16**:250, 1912.

5. Petersen, W. F.: The Ferment Antiferment Balance and Its Relation to Therapeusis, Arch. Int. Med. **20**:515 (Oct.) 1917.

6. Lange, F.: Experimentelle Untersuchungen über das Varhalten der Leukocyten nach Injektion von Bakterienextrakten, Deutsch. Arch. f. klin. Med. **94**:552, 1908.

7. Scully, F. T.: The Reaction After Intravenous Injections of Foreign Proteins, J. A. M. A. **69**:20 (July 7) 1917.

8. Gow, A. E.: Concerning Protein Shock in Intravenous Vaccine Therapy, St. Barth. Hosp. J. **25**:75, 1918-1919.

9. Spangler, R. H.: Eosinophilia Produced by Hypodermic Injections of Crotalin Solution, New York M. J., Oct. 4, 1913.

Leukocytic reactions, as well as temperature responses, depend, of course, on types of infections, synchronous conditions of the patients and finally, but not last, on the dosage and chemical nature of the particular protein agents employed, besides individual reactive differences.

In this work, eight agents were used, viz., distilled water, autoserum, horse serum, certified milk, market milk, crotalin, peptone and typhoid vaccine. By employing accepted doses and using normal subjects and rabbits, in these experiments, a favorable approach has seemed to have been made to the study of the relative values of these protein agents used in producing nonspecific biologic reactions.

PURPOSE OF INVESTIGATION

In view of the growing practical importance of protein therapy, particularly for the production of initial nonspecific resistance in diseases of bacterial origin, such as arthritis, acute or chronic, gonorrhea, typhoid fever and anthrax, the question of using the right protein agents for appropriate cases has offered a new field for research. In this work, a series of comparative studies were undertaken, in which various agents commonly employed in clinical and experimental work were used. Different biologic methods were employed.

There are, in these studies, four distinct objects in view:

1. To study comparatively the influence of various nonspecific protein agents on the reactive temperature.

2. To study comparatively the influence of various nonspecific protein agents on the mobilization of peripheral blood leukocytes.

3. To study comparatively the influence of various nonspecific protein agents on the mobilization of blood antibodies.

4. To study comparatively the influence of various nonspecific protein agents on the mobilization of blood enzymes.

The results of the first two of these studies concerning temperature and leukocytes are summarized in this paper; the results of those concerning blood antibodies and blood enzymes are given in two succeeding papers.

TECHNIC

All the agents employed, except the distilled water, were of some form of proteins:

1. Sterile distilled water.

2. Autoserum, separated from the blood of the same person or rabbit, after being placed for four hours in the refrigerator.

3. Normal horse serum, the stock serum, prepared by Mulford Laboratory for the use in therapeutic purposes.

4. Certified milk, with a bacterial count of not more than 10,000 per cubic centimeter. The milk was boiled at 100 degrees C. for ten minutes.

5. Market milk, with a bacterial count of between 300,000 and 400,000 per cubic centimeter. It was likewise boiled for ten minutes.

6. Crotalin, in solution, kindly supplied by Dr. Spangler of Philadelphia.

7. One per cent. peptone solution in saline, autoclaved for twenty minutes.

8. Typhoid vaccine, suspended in saline solution, with 100,000,000 per cubic centimeter.

All normal persons and rabbits were carefully weighed before the injection, and the amount of agent given was in proportion to their body weights, as follows:

(*a*) Sterile distilled water: 0.1 c.c. per kilogram of weight for human being; 1 c.c. per kilogram of weight for rabbit, given intravenously.

(*b*) Autoserum: 0.5 c.c. per kilogram of weight for human being and rabbit, given intravenously.

(*c*) Sterile normal horse serum: 0.2 c.c. per kilogram for human being and rabbit, given intravenously.

(*d*) Certified milk: 0.2 c.c. per kilogram of weight for human being and rabbit, given intramuscularly.

(*e*) Market milk: 0.2 c.c. per kilogram of weight for human being and rabbit, given intramuscularly.

(*f*) Crotalin: $\frac{1}{15,000}$ grain per kilogram of weight for human being; $\frac{1}{3,000}$ grain per kilogram of weight for rabbit, given hypodermically.

(*g*) Peptone solution (1 per cent.): 0.02 c.c. per kilogram of weight for human being and rabbit, intravenously.

(*h*) Typhoid vaccine (100,000,000 per cubic centimeter): 0.2 c.c. per kilogram of weight for human being and rabbit, intravenously.

Total leukocyte counts, differential counts and temperature observations were made just before, and four hours and twenty-four hours after the administration of the agents.

To avoid the effect of food on the temperature and leukocytic fluctuation, all examinations were made in the early part of the morning before any food was given.

A number of normal persons and rabbits also were similarly examined under the same condition for controls, and the composite results were obtained for comparison.

RESULTS

The composite results of the experiments are expressed in the accompanying tables and Charts 1 to 5, and the study may be briefly summarized as follows:

Influence on Temperature.—Variations of febrile reactions in various individuals were not infrequently observed but, in general, the adminis-

TABLE 1.—*Influence of Various Agents on Temperature*

Agents	Times Examinations Were Made	Temperature in Degrees Fahrenheit: Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	102.1	97.6	99.9	100.0
	4 hours after injection	103.0	98.8	100.9	101.0
	24 hours after injection	102.0	98.0	100.0	100.1
Autoserum	Before injection	101.9	97.0	99.5	100.0
	4 hours after injection	103.6	98.0	100.8	101.3
	24 hours after injection	101.5	97.0	99.3	99.8
Horse serum	Before injection	101.8	97.0	99.8	100.0
	4 hours after injection	102.1	98.4	100.3	100.5
	24 hours after injection	102.0	98.2	100.1	100.3
Certified milk	Before injection	102.1	99.2	100.2	100.0
	4 hours after injection	102.8	99.6	101.2	101.0
	24 hours after injection	101.4	99.1	100.3	100.1
Market milk	Before injection	102.2	98.6	100.4	100.0
	4 hours after injection	103.6	100.2	101.9	101.5
	24 hours after injection	103.0	100.0	101.5	101.1
Crotalin	Before injection	101.3	98.1	99.7	100.0
	4 hours after injection	102.6	98.6	100.6	100.9
	24 hours after injection	102.3	97.6	100.0	100.3
Peptone	Before injection	101.8	97.8	99.8	100.0
	4 hours after injection	103.3	100.2	101.8	102.0
	24 hours after injection	101.5	96.6	99.1	99.3
Typhoid vaccine	Before injection	102.0	98.6	100.3	100.0
	4 hours after injection	103.9	101.4	102.7	102.4
	24 hours after injection	101.7	100.2	101.0	100.7
Control	First examination	101.9	97.6	99.8	100.0
	Second examination	102.1	98.2	100.2	100.4
	Third examination	101.8	98.0	99.9	100.1

* Temperature taken before injection is arbitrarily set at 100 F. Increase or decrease of two subsequent observations is then added to or subtracted from it.

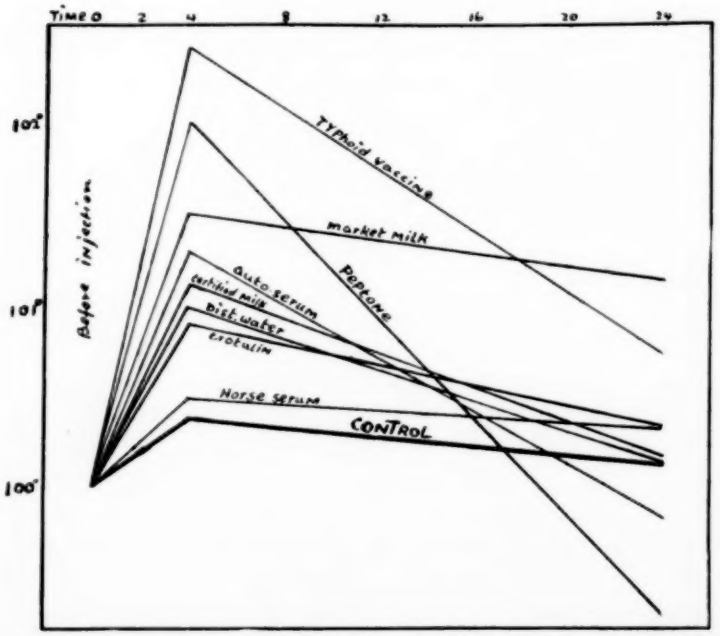

Chart 1.—Composite results of influence of various agents on temperature.

TABLE 2.—*Influence of Various Agents on Total Leukocyte Counts*

Agents	Times Examinations Were Made	Number of Cells per C.Mm. of Blood: Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	8,750	8,200	8,475	8,000
	4 hours after injection	7,600	7,600	7,600	7,125
	24 hours after injection	8,700	9,000	8,850	8,375
Autoserum	Before injection	8,900	8,200	8,550	8,000
	4 hours after injection	10,700	8,600	9,650	9,100
	24 hours after injection	9,500	8,400	8,950	8,400
Horse serum	Before injection	10,600	8,200	9,400	8,000
	4 hours after injection	13,400	7,600	10,500	9,100
	24 hours after injection	9,350	8,000	8,675	7,275
Certified milk	Before injection	4,200	8,320	6,260	8,000
	4 hours after injection	7,200	7,200	7,200	8,940
	24 hours after injection	3,200	8,210	5,705	7,430
Market milk	Before injection	7,770	8,850	8,310	8,000
	4 hours after injection	8,000	8,200	8,100	7,800
	24 hours after injection	13,100	12,000	12,550	12,240
Crotalin	Before injection	5,800	8,800	7,800	8,000
	4 hours after injection	7,000	8,200	7,600	7,800
	24 hours after injection	6,400	9,000	8,200	8,400
Peptone	Before injection	8,650	7,580	8,115	8,000
	4 hours after injection	8,200	7,320	7,760	7,645
	24 hours after injection	9,500	8,000	8,750	8,635
Typhoid vaccine	Before injection	9,200	10,400	9,800	8,000
	4 hours after injection	12,500	9,500	11,000	9,200
	24 hours after injection	15,800	9,000	12,400	10,800
Control	First examination	8,400	8,200	8,300	8,000
	Second examination	8,350	8,500	8,425	8,125
	Third examination	8,450	7,600	8,025	7,625

* The count taken before injection is arbitrarily set at 8,000. Increase or decrease of two subsequent counts is added to or subtracted from it.

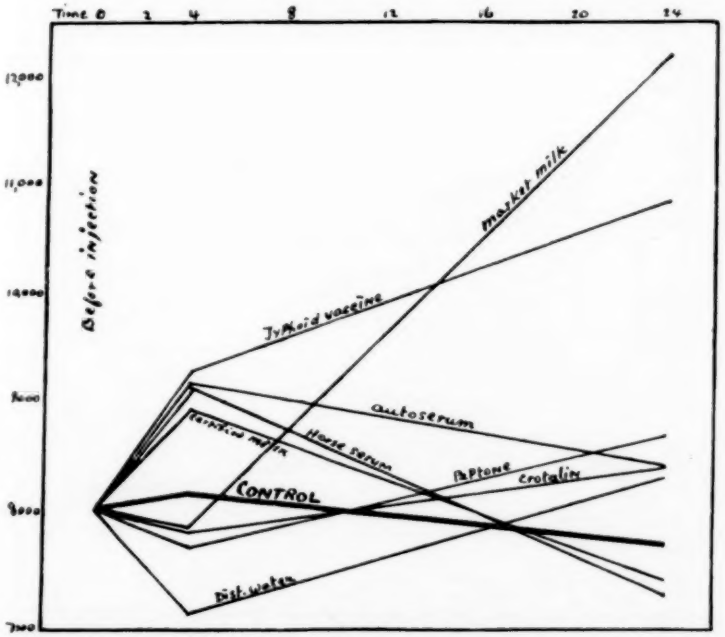

Chart 2.—Composite results of influence of various agents on total leukocyte count.

TABLE 3.—*Influence of Various Agents on Neutrophilic Polymorphonuclears*

Agents	Times Examinations Were Made	Number of Cells per C.Mm. of Blood			
		Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	3,500	3,162	3,330	5,000
	4 hours after injection	4,100	3,509	3,840	5,510
	24 hours after injection	1,914	4,410	3,160	4,830
Autoserum	Before injection	2,848	5,740	4,290	5,000
	4 hours after injection	4,654	6,708	5,680	6,390
	24 hours after injection	1,805	5,712	3,760	4,470
Horse serum	Before injection	5,194	6,232	5,710	5,000
	4 hours after injection	4,422	5,258	4,840	4,130
	24 hours after injection	5,300	6,400	5,850	5,140
Certified milk	Before injection	1,092	5,229	3,160	5,000
	4 hours after injection	2,880	4,608	3,740	5,580
	24 hours after injection	256	5,576	2,920	4,760
Market milk	Before injection	3,108	5,487	4,300	5,000
	4 hours after injection	4,640	5,576	5,110	5,810
	24 hours after injection	6,701	8,880	7,790	8,490
Crotalin	Before injection	2,088	6,864	4,480	5,000
	4 hours after injection	2,275	5,904	4,090	4,610
	24 hours after injection	2,120	6,120	4,120	4,640
Peptone	Before injection	1,081	4,700	2,890	5,000
	4 hours after injection	4,838	5,856	5,350	7,460
	24 hours after injection	2,116	5,856	3,990	6,100
Typhoid vaccine	Before injection	2,608	5,840	4,250	5,000
	4 hours after injection	1,537	7,410	4,470	5,220
	24 hours after injection	7,979	7,380	7,680	8,430
Control	First examination	2,280	5,600	3,940	5,000
	Second examination	2,980	5,660	4,320	5,380
	Third examination	2,366	5,320	3,843	4,908

* The count taken before injection is arbitrarily set at 5,000. Increase or decrease of two subsequent counts is added or subtracted from it.

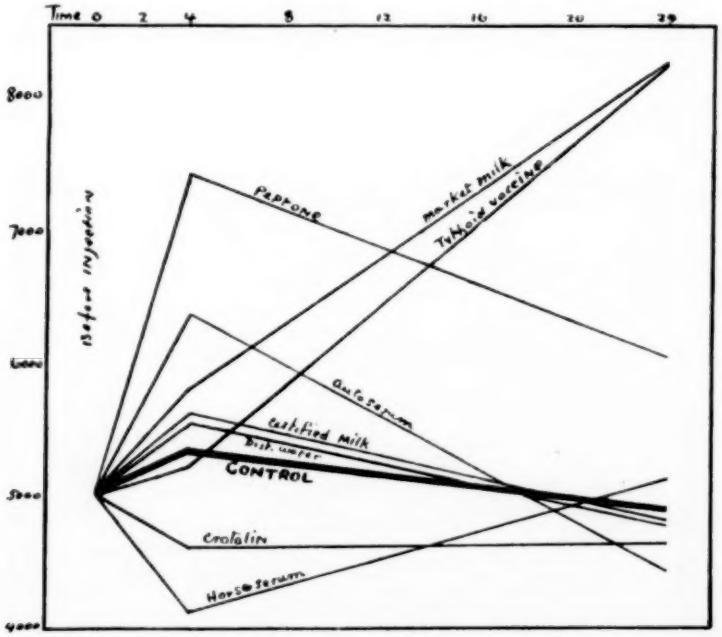

Chart 3.—Composite results of influence of various agents on neutrophilic polymorphonuclears.

TABLE 4.—*Influence of Various Agents on Lymphocytes*

Agents	Times Examinations Were Made	Number of Cells per C.Mm. of Blood: Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	4,080	3,200	3,640	2,000
	4 hours after injection	2,964	4,408	3,690	2,050
	24 hours after injection	4,090	4,032	4,160	2,520
Autoserum	Before injection	4,984	1,968	3,480	2,000
	4 hours after injection	5,243	1,032	3,140	1,660
	24 hours after injection	4,750	1,260	3,000	1,520
Horse serum	Before injection	4,604	2,640	3,620	2,000
	4 hours after injection	5,470	3,040	4,250	2,630
	24 hours after injection	3,114	1,960	2,540	920
Certified milk	Before injection	2,520	2,322	2,420	2,000
	4 hours after injection	1,870	1,440	1,660	1,240
	24 hours after injection	2,668	1,970	2,320	1,900
Market milk	Before injection	4,118	1,770	2,940	2,000
	4 hours after injection	2,480	1,470	1,980	1,040
	24 hours after injection	3,144	1,920	2,530	1,560
Crotalin	Before injection	2,726	1,940	2,330	2 000
	4 hours after injection	3,290	2,115	2,700	2,370
	24 hours after injection	2,584	1,800	2,190	1,860
Peptone	Before injection	4,022	1,880	3,220	2,000
	4 hours after injection	2,578	1,885	2,130	910
	24 hours after injection	3,725	1,200	2,460	1,240
Typhoid vaccine	Before injection	5,152	2,910	4,030	2,000
	4 hours after injection	4,250	2,090	3,160	1,130
	24 hours after injection	6,320	1,260	3,790	1,760
Control	First examination	4,260	1,840	3,050	2,000
	Second examination	4,330	1,990	3,160	2,110
	Third examination	4,807	1,900	3,350	2,300

* The count taken before injection is arbitrarily set at 2,000. Increase or decrease of two subsequent counts is added to or subtracted from it.

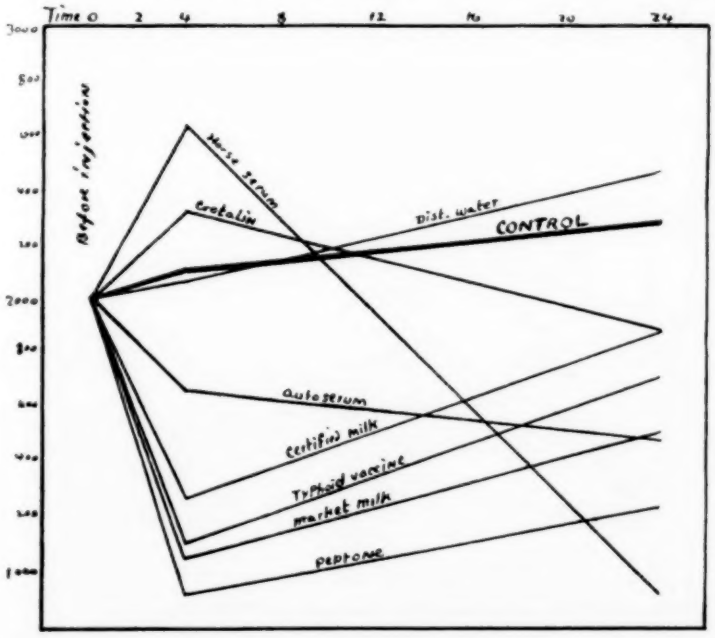

Chart 4.—Composite results of influence of various agents on lymphocyte count.

TABLE 5.—*Influence of Various Agents on Eosinophilic Polymorphonuclears*

Agents	Times Examinations Were Made	Number of Cells per C.Mm. of Blood			
		Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	250	124	190	200
	4 hours after injection	228	208	220	230
	24 hours after injection	535	70	300	310
Autoserum	Before injection	356	144	250	200
	4 hours after injection	856	65	460	410
	24 hours after injection	570	168	370	330
Horse serum	Before injection	212	120	170	200
	4 hours after injection	1,080	150	620	650
	24 hours after injection	186	40	110	140
Certified milk	Before injection	84	62	70	200
	4 hours after injection	440	36	240	370
	24 hours after injection	128	02	100	230
Market milk	Before injection	221	44	130	200
	4 hours after injection	640	116	330	400
	24 hours after injection	40	90	70	140
Crotalin	Before injection	116	9	60	200
	4 hours after injection	900	30	470	610
	24 hours after injection	65	50	60	200
Peptone	Before injection	256	35	150	200
	4 hours after injection	656	40	350	400
	24 hours after injection	240	60	650	700
Typhoid vaccine	Before injection	92	20	60	200
	4 hours after injection	250	26	140	280
	24 hours after injection	158	96	130	270
Control	First examination	160	40	100	200
	Second examination	476	20	248	348
	Third examination	280	90	185	285

* The count taken before injection is arbitrarily set at 200. Increase or decrease in two subsequent counts is added or subtracted from it.

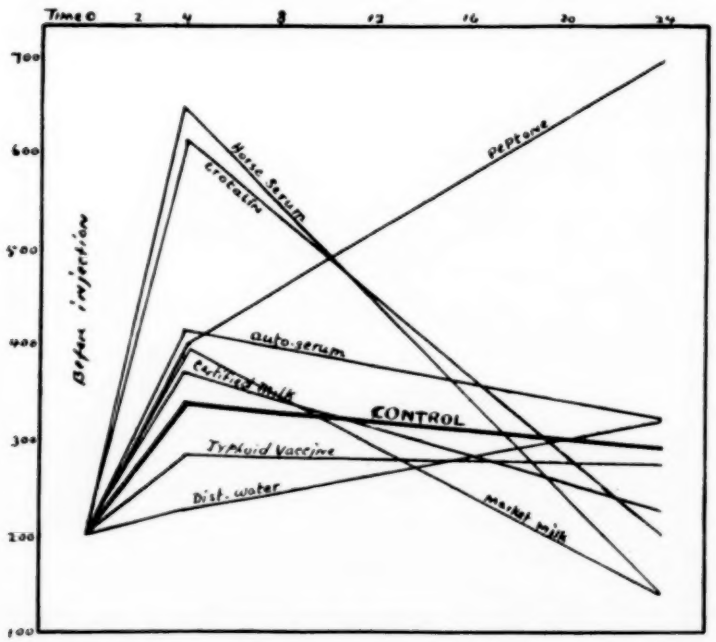

Chart 5.—Composite results of influence of various agents on eosinophilic polymorphonuclears.

tration of all protein agents was usually followed, within four hours, by distinct elevation of temperature, with a return to normal or about normal in twenty-four hours. *Bacillus typhosus*, peptone and market milk gave the most prompt initial temperature reaction, while that produced by market milk seemed to persist longer than that of other agents (Table 1 and Chart 1).

Influence on Total Leukocyte Count.—The leukocytic response was similar to temperature disturbances as far as the irregularities of the results are concerned. Market milk and *B. typhosus* were far more efficient in inducing a pronounced and persistent increaase of total leukocyte count (Table 2 and Chart 2).

Influence on Neutrophilic Polymorphonuclears.—Absolute increase of neutrophils apparently kept pace more closely with that of temperature than that of total counts. Market milk and typhoid vaccine produced, both in human being and rabbit, a most steady and persistent neutrophilic response, though peptone gave a prompter initial reaction (Table 3 and Chart 3).

Influence on Lymphocytes.—Under the influence of horse serum, crotalin and distilled water, the lymphocytes were found slightly increased during the first stages of leukocytic reaction, while those administered with peptone, market milk, typhoid vaccine or certified milk showed a decided drop during the same period. The usual or normal level was generally recovered, however, in about twenty-four hours (Table 4, Chart 4).

Influence on Eosinophilic Polymorphonuclears.—All rabbits invariably showed a slight increase after treatment. It was less so in the human beings. Peptone, horse serum and crotalin seemed to produce a decided eosinophilia.

CONCLUSIONS

1. All the agents used, including distilled water, autoserum, horse serum, certified milk, market milk, crotalin, peptone and typhoid vaccine, raise the temperature in normal persons or rabbits from 0.5 to 2.4 F., sometime within or about four hours after administration. The most decided rise is produced by typhoid vaccine, peptone, market milk and autoserum, named in the order of their effectiveness.

2. Peripheral blood leukocytes are more or less mobilized by all the agents used.

(*a*) Persistent leukocytosis is found after being treated with market milk or typhoid vaccine, named in the order of their effectiveness.

(*b*) Persistent increase of neutrophilic polymorphonuclears is found in those treated with market milk, typhoid vaccine and peptone.

(*c*) Persistent lymphocytosis is found in those treated with distilled water and crotalin.

(*d*) Persistent eosinophilia is seen in those treated with peptone solution.

TRANSIENT CHANGE IN THE AURICULOVENTRICULAR CONDITION FOLLOWING THE INJECTION OF HISTAMIN *

HIROTOSHI HASHIMOTO, M.D.
Fellow of the Rockefeller Foundation; Special Student in Medicine, the Mayo Foundation
ROCHESTER, MINN.

During the course of certain clinical studies in the medical service of the Mayo Clinic with regard to the use of histamin in various types of hypertension, it was observed that, not infrequently, arrhythmia followed the hypodermic injection of 0.5 mg. of histamin dichlorid. Since histamin dichlorid was found by Barger and Dale [1] and by Ackermann and Kutscher [2] to be one of the ergot bases which are capable of causing intense tonic contraction of the uterus, attempts have been made to use it in the field of gynecology for the treatment of uterine inertia. Jäger [3] observed palpitation of the heart in the shocklike condition induced by a hypodermic administration of from 6 to 8 mg. of histamin hydrochlorid to adults. Schenk [4] noted that following the subcutaneous administration of histamin phosphate, in doses of from 4 to 5 mg., the pulse rate was doubled, with a marked fall in the blood pressure. However, there are no clinical observations on record of arrhythmia due to administration of histamin.

Dale and Laidlaw [5] found, in experiments on cats kept under artificial respiration after the chest had been opened, that immediately following the intravenous injection of a large dose of histamin transient distention of the right side of the heart occurred with weakened and irregular contractions of the right ventricle, and that in an extreme case there was ventricular fibrillation, leading to the death of the animal. They considered the distention of the right side of the heart due to the constriction of the pulmonary arteries. In an experiment on

* This work was done under the supervision of Dr. F. A. Willius.

1. Barger, G., and Dale, H. H.: The Presence in Ergot and Physiological Activity of B-Imidazolylethylamine, J. Physiol. **40**:xxxviii-xl, 1910; Chemical Structure and Sympathomimetic Action of Amines, J. Physiol. **42**:19-59, 1910.

2. Ackermann, D., and Kutscher, F.: Untersuchungen über die physiologische Wirkung einer Secalebase und des Imidazolyläthylamins, Ztschr. f. Biol. **54**:387-394, 1910.

3. Jäger, F.: Ein neuer, für die Praxis brauchbarer Sekaleersatz (Tenosin), München. med. Wchnschr. **2**:1714-1715, 1913.

4. Schenk, P.: Ueber die Wirkungsweise des B-Imidazolyläthylamins (Histamin) auf den menschlichen Organismus, Arch. f. exper. Path. u. Pharmakol. **89**:332-339, 1921.

5. Dale, H. H., and Laidlaw, P. P.: Histamin Shock, J. Physiol. **52**: 355-390 (March) 1919.

the heart-lung preparation from a dog, Führer and Starling [6] observed that on adding histamin to the circulating blood, the heart soon failed and dilated, and the pressure rose in the left auricle. Einis [7] found, in the isolated frog's heart, that small doses of histamin induced slowed and slightly intensified contraction of the heart, while large doses caused periodic cessation of the contraction, which produced a type of contraction of the heart comparable with "group contraction" of Luciani. On the isolated heart of the rabbit, perfused with Ringer's solution by the

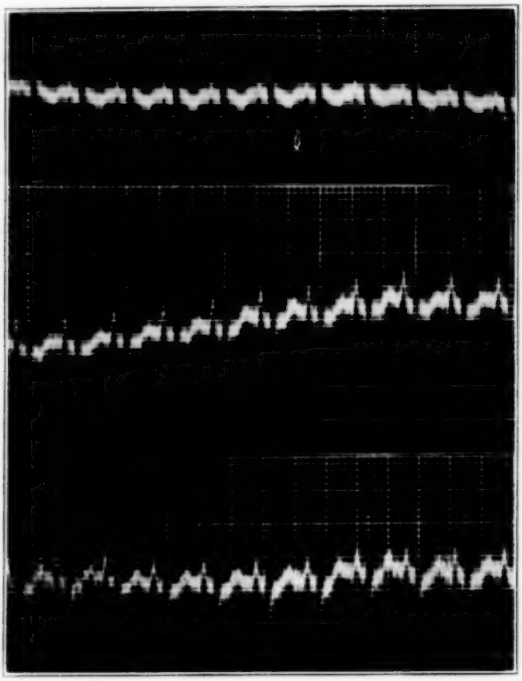

Fig. 1 (Experiment 1).—Electrocardiograms taken with intact vagi, under ether anesthesia, before histamin injection. Derivation I, P-R interval, 0.08 second; heart rate, 205 each minute; T wave inverted. Derivation II, P-R interval, 0.08 second; heart rate, 200 each minute. Derivation III, P-R interval, 0.08 second; heart rate, 187 each minute.

use of Langendorff's apparatus, Einis observed that 0.5 c.c. of 0.1 per cent. solution of histamin caused quickening of the heart rate to nearly

6. Führer, H., and Starling, E. H.: Experiments on the Pulmonary Circulation, J. Physiol. **47**:286-304, 1913-1914.

7. Einis, W.: Ueber die Wirkung des Pituitrins und B-Imidazoläthylamins (Histamins) auf die Herzaktion, Biochem. Ztschr. **52**:96-117, 1913.

three times normal, with increased excursions of the heart action, which were later followed by slowing of the rate to less than the original. At the summit of this stimulating effect of the histamin, often extrasystoles supervened, each extrasystole being of about half the extent in excursion of immediately preceding systoles. In some of the similar experiments, he found, furthermore, that alternate auricular contractions were not followed by the ventricular contraction, and finally the ventricle ceased to respond to the auricular contractions, which were still progressing. He believed that this phenomenon was due to impaired auriculoventricular conduction. In another series of his experiments, made on rabbit's heart perfused with hirudinized blood, however, he failed to demonstrate

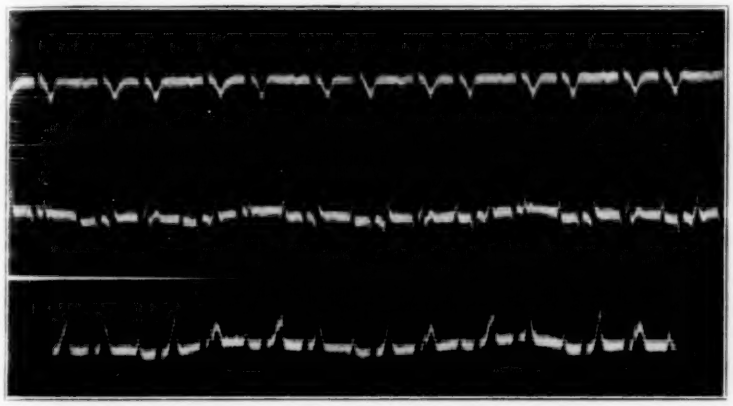

Fig. 2 (Experiment 1).—Electrocardiograms taken from one to six minutes following intravenous injection of 2 mg. of histamin dichlorid for each kilogram of body weight. Complete auriculoventricular dissociation. Derivation I (from one to two minutes after injection of histamin), P-R interval variable; T wave inverted; auricular rate, 200 each minute, and ventricular rate, 133 each minute. Derivation II (from three to four minutes after injection of histamin), P-R interval variable; T wave inverted; auricular rate, 197 each minute, and ventricular rate, 125 each minute. Derivation III (five to six minutes after injection of histamin), P-R interval variable; Q-R-S complex notched; auricular rate, 193 each minute, and ventricular rate, 129 each minute.

the heart block, but saw only the quickening of the rate with increased excursion of the heart action which had been preceded by the slowing of slight degree and short duration. He regarded the quickening of the rate as an important part of the effect of histamin on the heart action, and thought that the slowing which follows the quickening in rabbit's heart perfused with Ringer's solution, might be due to exhaustion of the organ, as such slowing was missed in the preparation perfused with hirudinized blood.

In order to throw more light on the obscure points concerning the effect of histamin on the heart action, I have studied this effect carefully by means of electrocardiographic records.

EXPERIMENTAL METHODS

Adult healthy dogs were employed for the experiments. To obtain electrocardiograms, the electrodes were applied to both forelegs and to the left hind leg. Some of the animals were anesthetized by ether, using the intratracheal insufflation method; others by a stomach tube, about one hour before the experiment, by the administration of from 1 to 1.5 gm. of urethan for each kilogram of body weight. In some animals under ether anesthesia, both vagi, as they lay in the carotid sheath, were divided, about thirty minutes before the experiment. In some animals with intact or divided vagi, atropin sulphate was injected intravenously

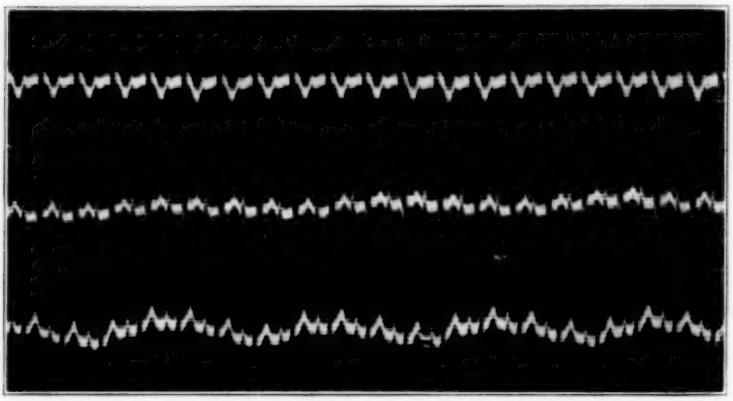

Fig. 3 (Experiment 1).—Electrocardiograms taken from eight to thirteen minutes after injection of histamin. Delayed auriculoventricular conduction and slowed heart rate. Derivation I (from eight to nine minutes after injection of histamin), P-R interval 0.16 second; T wave inverted, and auricular and ventricular rates the same, 191 each minute. Derivation II (from ten to eleven minutes after injection of histamin), P-R interval, 0.14 second, and auricular and ventricular rates the same, 191 each minute. Derivation III (from twelve to thirteen minutes after injection of histamin), P-R interval, 0.12 second; Q-R-S complex notched; auricular and ventricular rates the same, 180 each minute.

in doses of from 0.065 to 0.156 mg. for each kilogram of body weight, for the purpose of paralyzing the vagi completely. The experiment on histamin was made at the period from four to twenty minutes after the injection of atropin.

A pure preparation of histamin dichlorid [8] was used. Two milligrams of this drug for each kilogram of body weight were dissolved in small

8. This was obtained through the courtesy of Dr. Milton T. Hanke.

amounts of physiologic salt solution and were injected into the leg vein of a dog, and proved to be so toxic as to cause a chain of symptoms resembling those of anaphylactic shock, that is, stupor, fall in body temperature, cyanosis or flushing of the mucous membrane and the skin, slowed, and later quickened, weak and arrhythmic pulse, labored, slowed,

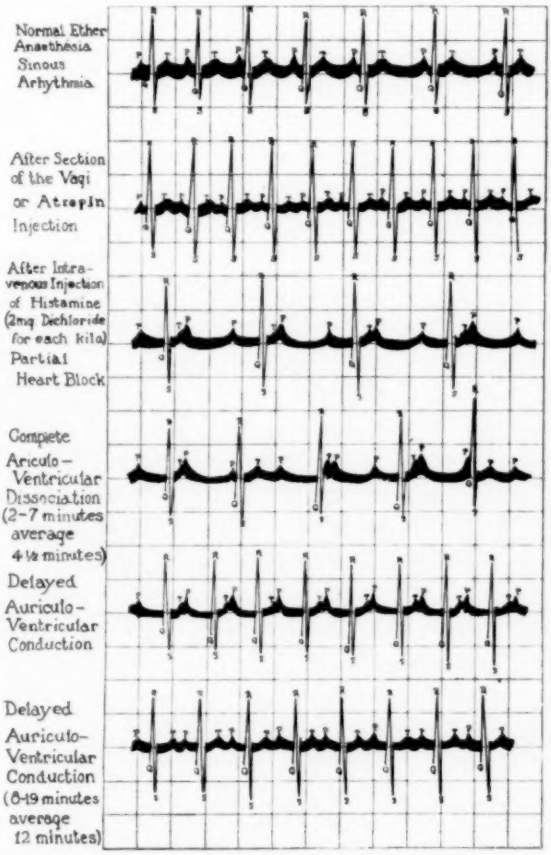
Normal Ether Anesthesia Sinous Arhythmia
After Section of the Vagi or Atropin Injection
After Intravenous Injection of Histamine (2mg Dichloride for each kilo) Partial Heart Block
Compiete Aricuto-Ventricular Dissociation (2-7 minutes average 4½ minutes)
Delayed Auriculo-Ventricular Conduction
Delayed Auricuto-Ventricular Conduction (6-19 minutes average 12 minutes)

Fig. 4.—Drawings of electrocardiograms.

and later weakened respiration, defecation or tenesmus, and retching or vomiting. The mercury manometer, attached to a cannulated artery of the animal anesthetized by ether, showed a prompt fall of arterial blood pressure to a point lower than 40 mm., immediately following the injection of histamin. The fall persisted for a period of from a half-hour to two hours. If not anesthetized with ether or urethan, the dogs

recovered nearly completely from the shocklike condition within from ten to thirty minutes. Slight anesthesia with ether or urethan, under which the animals were kept during the procedure of taking the electrocardiograms, more or less intensified the intoxication, but most of the animals recovered within one or two hours.

EXPERIMENTAL OBSERVATIONS

EXPERIMENT 1.—Dog 1, a male, adult mongrel, weighing 6.34 kg., with intact vagi, received 13 mg. of histamin dichlorid, dissolved in 10 c.c. of physiologic sodium chlorid solution, injected intravenously. The animal remained under ether anesthesia while the electrocardiograms were taken (Table 1).

Complete auriculoventricular dissociation occurred from one to six minutes after the injection. In the electrocardiogram taken at this period, the auricular rate was almost unchanged; the P waves occurred at regular intervals, but they bore no regular relationship to the Q-R-S complexes. The ventricular rate was markedly slowed to less than two-thirds of the auricular and was arrhythmic. Exaggerated S waves in Lead III indicated the preponderance of the left ventricle. At the period of from eight to thirteen minutes after the injection of histamin, the P-R intervals became constant, but evidently much prolonged. The Q-R-S complexes were notched and still directed downward in Lead III. The electrocardiograms taken later than twenty-eight minutes after the injection showed nothing abnormal except a slightly slowed heart rate (Figs. 1, 2 and 3).

EXPERIMENT 2.—Dog 2, a female mongrel, weighing 6.18 kg., with both vagi divided, under ether anesthesia, thirty minutes before the taking of the electrocardiogram, during which little ether was added, was injected intravenously with 12 mg. of histamin dichlorid in 10 c.c. of physiologic sodium chlorid solution.

In the electrocardiogram (Table 2) taken from one to four minutes after the injection, the auricular rate was slowed, but was not arrhythmic. The P-R intervals were strikingly prolonged, and here and there the P wave was not followed by the ventricular complex which should respond to it, that is, delayed auriculoventricular conduction with partial heart block. The P wave in Lead II was notched, but not changed in its amplitude. At the end of the period of eight minutes after the injection, the conduction time returned to the original length.

EXPERIMENT 3.—Dog 3, a male mongrel, weighing 6 kg., was given 6 gm. of urethan by stomach tube, one hour before the experiment. Both vagi were cut, under slight ether anesthesia. Twelve milligrams of histamin dichlorid in 8 c.c. of physiologic sodium chlorid solution was injected intravenously.

In the electrocardiogram (Table 3) taken from one to two minutes after the injection, there were evidences indicative of partial heart block. The P waves occurred at regular, but prolonged intervals. The Q-R-S complexes following every second P wave, however, were absent in the first portion of the tracing, in its middle portion following every third P wave, and in the latter portion following every fourth to sixth P wave. In the electrocardiogram taken later than six minutes after the injection, there was slight prolongation of the P-R intervals which returned to normal within about ten minutes after the injection, and slightly slowed heart rate, but no auriculoventricular dissociation was noticeable after this.

EXPERIMENT 4.—Dog 4, a male, adult poodle, weighing 10.85 kg., had both vagi divided, under ether anesthesia, thirty minutes before the experiment. The animal, having been well trained, needed no anesthesia for the taking of electrocardiograms. Fourteen milligrams of histamin dichlorid, dissolved in 6 c.c. of physiologic sodium chlorid solution, was injected intravenously.

TABLE 1.—*Results in Experiment 1*

			Electrocardiogram										
			Intervals, Second			Amplitude, Millivolt					Rate		
April 29, 1924	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V	Remarks
Before injection of histamin	1	I	0.08	0.03	0.13	3	5	11	0	—2	205	205	
	1	II	0.08	0.03	0.17	5	2	14	5	4	200	200	
	1	III	0.08	0.04	0.16	4.5	0	12	6	4	187	187	
After injection of histamin													
From 1 to 2 minutes	2	I	0.16-0.24	0.04	0.14	3	6	12	0	—5	200	133	Complete auriculoventricular dissociation. Left ventricular preponderance. Respiration slowed and labored
3 to 4 minutes	2	II	0.20-0.26	0.04	0.14	5	3.5	9	5	—3.5	197	125	
5 to 6 minutes	2	III	0.16-0.28	0.05	0.16	5	0	5	9	6	193	129	
8 to 9 minutes	3	I	0.16	0.04	0.18	3	6	15	0	—4.5	191	191	Delayed auriculoventricular conduction. Notched Q-R-S in Lead III. Left ventricular preponderance
10 to 11 minutes	3	II	0.14	0.04	0.16	5	6.5	14	0	4	191	191	
12 to 13 minutes	3	III	0.12	0.05	0.14	5	0	3	8	4.5	180	180	
15 to 19 minutes	4	II	0.09	0.04	0.12	4.5	5	7.5	4	—3	175	175	
28 minutes.....	5	II	0.08	0.04	0.12	4	4	8	4	—3	180	180	
	5	II	0.08	0.03	0.12	5	4	8	4	—3.5	171	171	
	5	II	0.08	0.04	0.12	4.5	4	7.5	4	—3.5	176	176	

TABLE 2.—*Results in Experiment 2*

			Electrocardiogram										
			Intervals, Second			Amplitude, Millivolt					Rate		
May 6, 1924	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V	Remarks
Before injection of histamin	1	I	0.11	0.05	0.17	4	5	12	2	—3	144	144	Notched Q-R-S; left ventricular preponderance
	1	II	0.11	0.05	0.16	6.5	4	15	5	—3	150	150	
	1	III	0.09	0.04	0.19	5	4	5	11	3	150	150	
After injection of histamin													
From 1 to 4 minutes	2	I	0.32	0.06	0.18	5	7	14	2	—4	135	109	Delayed auriculoventricular conduction. Periods of partial heart block, 2:1. Notched P in Lead II; slurred or notched Q-R-S in all leads; left ventricular preponderance; labored respiration; salivation
	2	II	0.26	0.06	0.16	4	6.5	9.5	4	—3	131	131	
	2	III	0.26	0.06	?	3	2	4	7	Trace	132	132	
5 to 8 minutes	3	I	0.13	0.05	0.16	4.5	7	12	0	—4	133	133	Slurred or notched Q-R-S; left ventricular preponderance
	3	II	0.12	0.05	0.17	5	6	13	2	—4	131	131	
	3	III	0.11	0.04	?	3	8	4	4	Trace	138	138	
10 to 13 minutes	4	I	0.12	0.05	0.16	4	5	10	2	—3	136	136	Slurred or notched Q-R-S; left ventricular preponderance
	4	II	0.13	0.05	0.17	3.5	4	10	4	—3	120	120	
	4	III	0.10	0.04	?	4	0	5	9	Trace	129	129	
15 to 18 minutes	5	I	0.10	0.04	0.16	4	6	12	0	—3	133	133	Slurred or notched Q-R-S; left ventricular preponderance
	5	II	0.12	0.04	0.16	5	4	10	4	—3	133	133	
	5	III	0.11	0.04	0.19	3	1	3	7	2	127	127	

In the electrocardiograms (Table 4), taken from fifteen seconds to one minute following the injection, the ventricular complexes that should have immediately followed every second P wave were absent. The auricular rate was slightly slowed and regular. The P-R intervals were prolonged though constant, that is, the partial heart block was in the rate of 2:1. At the period of from one and one-fourth to five and one-fourth minutes, the electrocardiograms showed that the P waves, although they occurred at regular intervals, bore no relationship to the ventricular complexes. The ventricular rate was slowed to about one-half of the auricular rate, and was more or less arrhythmic. In the electrocardiograms taken from seven and one-half to eight and three-fourths minutes after the injection, the P-R intervals were slightly prolonged, and the rate of both auricular and ventricular contractions was more or less slowed, but no dissociation between them was apparent. More than eleven minutes after the injection, there was nothing abnormal, except a slightly slowed heart rate.

EXPERIMENT 5.—Dog 5, a male, adult mongrel, weighing 5 kg., had both vagi divided, under procain anesthesia, a half-hour before the experiment. No anesthesia was induced during the taking of the electrocardiograms. Ten milligrams of histamin dichlorid, dissolved in 5 c.c. of physiologic sodium chlorid solution, was injected intravenously.

The occurrence of complete auriculoventricular dissociation was indicated by electrocardiography (Table 5) from one-fourth to five and one-half minutes following the injection. Although the P waves occurred at regular intervals and in the rate nearly similar to that before the injection, they did not keep constant relation to the ventricular complexes. Within one minute after the injection, the ventricular rate was slowed to about one-half the auricular rate, but later it was gradually quickened, so that toward the end of five minutes it nearly equaled the auricular rate. The ventricular contractions were more or less arrhythmic, while the auricular were very regular. The tracing taken later, at from nine to ten minutes after the injection, showed slightly prolonged P-R intervals, but no further abnormal changes.

EXPERIMENT 6.—Dog 6, a male, adult mongrel, weighing 5.56 kg., had both vagi cut, under ether anesthesia, thirty minutes before the experiment. No more ether was given during the taking of the electrocardiograms. Eleven milligrams of histamin dichlorid, dissolved in 6 c.c. of physiologic sodium chlorid solution, was injected into the leg vein.

In the electrocardiograms (Table 6) taken from one-half to one and three-fourths minutes after the injection, the P waves, although occurring at regular intervals, bore no relationship to the Q-R-S complexes, the P-R intervals showing great variation. Although the auricular rate was not much changed, compared with that before the injection, the ventricular rate was slowed to the extent of nearly two thirds of the auricular rate, and was slightly arrhythmic. In the tracing taken from one and three-fourths to four minutes after the injection, there was slight prolongation of the P-R intervals and slight slowing of both the auricular and ventricular rates, but no auriculoventricular dissociation was indicated.

EXPERIMENT 7.—Dog 7, a female, adult mongrel, weighing 8 kg., was electrocardiographed with the vagus intact.

The animal was kept under ether anesthesia during the taking of the electrocardiograms (Table 7). For the purpose of paralyzing the vagus, 0.5 mg. of atropin sulphate, dissolved in 4 c.c. of physiologic sodium chlorid solution, was injected intravenously. Four minutes later, when the effect of atropin had evidently been indicated on the electrocardiograph, 16 mg. of histamin dichlorid, dissolved in 4 c.c. of physiologic sodium chlorid solution, was injected intravenously. Before the injection of atropin, the dog showed sinus arrhythmia. All complexes in the tracings were found to maintain their proper relationship to one another, but there was a cyclic variation of the heart rate from 200 to 240, or from 143 to 214.

TABLE 3.—*Results in Experiment 3*

July 14, 1924	Number	Lead	Electrocardiogram: Intervals, Second P-R	Q-R-S	S-T	Amplitude, Millivolt P	Q	R	S	T	Rate A	V	Remarks
Before injection of histamin	1	I	0.08	0.04	0.11	1.5	3	3	0	—1	250	250	Notched Q-R-S in Lead III. Left ventricular preponderance
	1	II	0.08	0.04	0.14	4	2.5	4	2	3	250	250	
	1	III	0.08	0.03	0.13	3.5	0	2	2	3	250	250	
After injection of histamin													
From 1 to 1.33 minutes	2	I	0.16	0.04	0.14	2	4	5	0	—2	185	92	
	2	II	0.16	0.04	0.15	2	4	5	0	—2	180	120	Partial heart block
1.67 to 2 minutes	2	II	0.14	0.04	0.14	2	4	5	0	—2	180	160	Notched Q-R-S in Lead III
	2	II	0.12	0.04	0.13	4	2	6	0.5	—1.5	193	193	
2.5 to 6.5 minutes	2	III	0.11	0.04	0.13	3	0	2	1.5	1.5	200	200	
6 to 6.5 minutes	3	I	0.11	0.04	0.12	2	4	5	0	—2	211	211	Notched Q-R-S in Lead III. Left ventricular preponderance
7 to 7.5 minutes	3	II	0.10	0.04	0.16	1	4.5	4	1.5	2.5	212	212	
8 to 8.5 minutes	3	III	0.09	0.05	0.13	3	0	1	3	3	216	216	
11 to 11.5 minutes	4	I	0.08	0.04	0.11	2	3	4	0	—2	225	225	Left ventricular preponderance
12 to 12.5 minutes	4	II	0.08	0.04	0.13	4	3	4	1.5	2	225	225	
13 to 13.5 minutes	4	III	0.08	0.04	0.12	3	0	1	3	3.5	225	225	Notched Q-R-S in Lead III
16.5 to 16.75 minutes	5	I	0.08	0.04	0.12	2	4	5	0	—2	220	220	
17 to 17.25 minutes	5	II	0.08	0.04	0.12	5	2.5	5.5	1.5	2.5	220	220	Notched Q-R-S in Lead III
17.5 to 17.75 minutes	5	III	0.08	0.04	0.12	3	0	1	2	3	220	220	

TABLE 4.—*Results in Experiment 4*

July 21, 1924	Number	Lead	Electrocardiogram: Intervals, Second P-R	Q-R-S	S-T	Amplitude, Millivolt P	Q	R	S	T	Rate A	V	Remarks
Before injection of histamin	1	I	0.06	0.03	0.09	1.0	1.5	3.0	0.0	—1.0	262	262	
	1	II	0.06	0.03	0.09	3.0	1.0	6.0	1.0	—1.5	262	262	Exaggerated P
	1	III	0.07	0.03	0.10	2.5	1.0	6.5	1.0	—1.0	262	262	
After injection of histamin													
From 0.25 to 0.50 minutes	2	I	0.18	0.03	0.18	1.0	2.0	3.5	1.0	—1.0	220	110	Partial heart block, 2:1. Respiration labored and frequent
0.75 to 1.0 minutes	2	II	0.18	0.03	0.18	2.5	0.0	6.0	1.0	3.5	230	116	
1.25 to 1.50 minutes	2	III	0.08-0.17	0.03	0.20	2.0	0.0	6.0	2.0	5.0	262	131	Defecation
	2	II	0.04-0.20	0.03	0.16	1.5	0.0	6.5	1.5	4.0	214	120	Salivation
	2	II	0.13-0.24	0.04	0.13	2.0	0.0	5.0	1.0	2.5	210	140	Complete A-V dissociation. Retching
1.75 to 5.25 minutes	2	II	0.12-0.24	0.03	0.14	2.0	0.0	4.5	1.0	2.0	207	157	
	2	II	0.12-0.26	0.03	0.14	2.0	0.0	4.5	1.0	2.0	212	183	Notched P and Q-R-S
	2	II	0.03-0.10	0.04	0.15	2.5	0.0	5.5	1.0	3.0	216	115	
7.50 to 7.75 minutes	3	I	0.14	0.02	0.10	0.5	1.0	2.0	0.5	—1.0	214	214	Notched P and Q-R-S
8.0 to 8.25 minutes	3	II	0.12	0.03	0.12	1.5	0.5	3.0	1.0	1.5	210	210	
8.50 to 8.75 minutes	3	III	0.12	0.03	0.12	1.0	0.0	3.0	1.5	1.5	212	212	
11.0 to 11.25 minutes	4	I	0.08	0.02	0.12	1.5	2.0	5.0	0.5	—2.0	230	230	
11.50 to 11.75 minutes	4	II	0.08	0.03	0.15	3.5	1.5	5.0	0.0	4.0	225	225	Exaggerated P
12.0 to 12.25 minutes	4	III	0.08	0.03	0.14	3.5	0.5	6.0	0.0	5.0	225	225	
16.0 to 16.25 minutes	5	I	0.07	0.02	0.12	1.5	2.0	4.5	0.0	—1.5	220	220	
16.5 to 16.75 minutes	5	II	0.06	0.03	0.12	2.0	0.0	3.0	1.0	3.5	220	220	Exaggerated P
17.0 to 17.25 minutes	5	III	0.06	0.03	0.12	3.0	0.0	4.5	1.5	2.5	225	225	

After the injection of atropin, sinus arrhythmia disappeared completely. The P-R intervals were slightly shortened, and the heart rate was accelerated. Immediately following the injection of histamin, the P-R intervals were markedly prolonged, and every second P wave was not succeeded by the ventricular complex. The ventricular rate was reduced to about one-half the auricular rate. This period of partial heart block was followed by a period of complete auriculoventricular dissociation. The P waves lost their proper relationship to the Q-R-S complexes, and the P-R intervals were variable. The ventricular rate, which had been much slowed, showed a tendency to approach the auricular rate. At the end of the period of eight minutes after the injection of histamin, there was no indication of the auriculoventricular dissociation, but the P-R intervals were still prolonged. As the accelerated rate had continued, the P waves were superimposed on, or buried in, the preceding ventricular complex. A part of the tracing, therefore, resembled that of nodal rhythm. Thirteen minutes after the injection, nothing abnormal was found in the tracing, except slightly prolonged P-R intervals and diminished amplitude of Q-R-S complexes. Absence of the sinus arrhythmia and presence of the accelerated rate suggested that there was still paralysis of the vagus induced by the atropin.

EXPERIMENT 8.—Dog 8, a female, adult mongrel, weighing 12.8 kg., had both vagi divided, under ether anesthesia, forty minutes before the experiment. For the purpose of paralyzing the vagi completely, 1 mg. of atropin sulphate, dissolved in 4 c.c. of physiologic sodium chlorid solution, was injected twice intravenously, with an interval of ten minutes. Twenty-six milligrams of histamin dichlorid, dissolved in 4 c.c. of physiologic sodium chlorid solution, was injected intravenously five minutes after the second injection of atropin.

During the taking of the electrocardiograms (Table 8), the animal was kept under ether anesthesia. There were no notable changes in the electrocardiogram after the injection of atropin. A continuous electrocardiographic tracing in the second derivation was taken, from one to ten minutes following the injection of histamin. From one to four minutes after, complete auriculoventricular dissociation occurred. The P waves occurred at regular intervals, but bore no relationship to the ventricular complexes, the P-R intervals being variable. The P waves often were superimposed on the R or T waves. Synchronous occurrence of the P waves with the R or the T waves was indicated by a conspicuously greater amplitude of the latter. The auricular rate was slightly slowed. The ventricular contractions were arrhythmic and of lower rate than the auricular. Toward the end of four minutes, the ventricular rate was approaching the auricular.

From five to seven minutes after the injection of histamin, both the auricular and the ventricular contractions occurred at the regular and the similar intervals. In the first part of this period, the P and the T waves occurred synchronously, producing single waves of comparatively high amplitude. In the last part of the period there was still the confluence of the P and the T waves, although their peaks were distinguishable from each other. From eight to ten minutes after the injection of histamin, nothing abnormal was noted, except a more or less lengthened conduction time.

EXPERIMENT 9.—Dog 9, a female, adult mongrel, weighing 10.7 kg., had both vagi divided, under ether anesthesia, thirty minutes before the experiment. During the taking of the electrocardiograms (Table 9), the animal was kept under ether anesthesia. One milligram of atropin sulphate, dissolved in 4 c.c. of physiologic sodium chlorid solution, was injected intravenously. Nine minutes later, 22 mg. of histamin dichlorid, dissolved in 2 c.c. of physiologic sodium chlorid solution, was injected intravenously. A continuous electrocardiographic record in the second derivation was taken from one-fourth to five and one-half minutes after the injection of histamin. Six minutes after the injection of atropin, there was a gradual decrease in amplitude of the P waves, as well as of the Q-R-S complexes. The R waves were slurred.

TABLE 5.—*Results in Experiment 5*

			Electrocardiogram										
			Intervals, Second			Amplitude, Millivolt					Rate		
July 22, 1924	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V	Remarks
Before injection of histamin	1	I	0.08	0.06	0.12	2	0	9	0.5	2	229	229	Slurred or notched Q-R-S in Leads I and II; exaggerated P in Leads II and III
	1	II	0.08	0.04	0.13	5	0	8	2	3	228	228	
	1	III	0.08	0.04	0.14	5.5	4	6	3	2	228	228	
After injection of histamin													
From 0.25 to 0.5 minutes	2	I	0.18	0.06	0.14	2	0	10	0	6	229	115	Partial heart block, 2:1
0.75 to 1 minute	2	II	0.18	0.05	0.20	5	4	7.5	0.5	6	229	115	
1.5 to 1.75 minutes	2	III	?	0.04	0.18	2	8	7	1	−3	233	150	Complete auriculoventricular dissociation
	2	II	?	0.04	0.16	4	2	4	1	±5	225	172	
2 to 5.5 minutes	2	II	?	0.04	0.16	3	2	8	0	−4	229	176	Restless a few seconds immediately following the injection, but later calm
	2	II	0.20-0.24	0.04	0.12	4	3	8	0	−4	225	200	
	2	II	0.20	0.04	?	4	3	7	1	?	232	230	Respiration slowed; salivation
9 to 9.25 minutes	3	I	0.11	0.04	0.12	2	1.5	6	0	1	225	225	Notched Q-R-S in Lead II
9.5 to 9.75 minutes	3	II	0.12	0.04	0.10	3	3	3	0	±2	229	229	Left ventricular preponderance
10 to 10.25 minutes	3	III	0.10	0.04	0.16	4	10	3	1	±3	218	218	
14 to 14.25 minutes	4	I	0.08	0.03	0.16	2	1	4	1	−3	214	214	
16.25 to 16.5 minutes	4	II	0.08	0.03	0.16	4	6	6	0	−3	210	210	Left ventricular preponderance
18 to 18.25 minutes	4	III	0.08	0.03	0.16	4	6	7	1	±3	214	214	
19 to 19.25 minutes	5	I	0.08	0.04	0.16	2	0.5	8	0	−3	218	218	Notched Q-R-S in Lead I
19.5 to 19.75 minutes	5	II	0.08	0.03	0.16	3	2	6	0	2	225	225	Left ventricular preponderance
20 to 20.25 minutes	5	III	0.08	0.03	0.14	2	6	6	0	−2	225	225	
24 to 24.25 minutes	6	I	0.08	0.04	0.15	2	0	7	0	2	225	225	Notched Q-R-S in Leads I and II
24.5 to 24.75 minutes	6	II	0.08	0.04	0.16	2	1	9	0	2	225	225	Left ventricular preponderance
25 to 25.25 minutes	6	III	0.08	0.04	0.16	4	6	9	1	2	225	225	

TABLE 6.—*Results in Experiment 6*

			Electrocardiogram										
			Intervals, Second			Amplitude, Millivolt					Rate		
July 23, 1924	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V	Remarks
Before injection of histamin	1	I	0.06	0.04	0.12	2	0	6	0	−0.5	220	220	Exaggerated P in Leads II and III
	1	II	0.05	0.04	0.16	4	0	11	0	−1	220	220	
	1	III	0.06	0.04	0.12	4	1	9	1	−1.5	220	220	
After injection of histamin													
From 0.5 to 0.75 minutes	2	I	0.10-0.16	0.03	0.16	2	1	6	1	2	220	133	Complete auriculoventricular dissociation; slurred Q-R-S in Lead III
1 to 1.25 minutes	2	II	0.12-0.17	0.04	0.16	4	1	10	1.5	±3	218	170	
1.5 to 1.75 minutes	2	III	0.12-0.18	0.03	0.12	3.5	0	5	1	−1.5	210	171	Urination; respiration slowed and labored
1.75 to 4 minutes	2	II	0.12	0.03	0.14	2.5	1	7	1	±2	195	195	
	2	II	0.10	0.03	0.14	2	0.5	7.5	1	±2	180	180	
	2	II	0.08	0.03	0.15	2	0.5	7	1	±2	180	180	
6.5 to 6.75 minutes	3	I	0.08	0.03	0.12	1	1	5	3	−2	240	240	
7 to 7.25 minutes	3	II	0.07	0.04	0.14	5	0	11	3	−4	250	250	Exaggerated P in Lead II
7.25 to 7.5 minutes	3	III	0.07	0.03	0.12	3.5	0	8	2	−2	250	250	
10.5 to 10.75 minutes	4	I	0.07	0.03	0.12	1.5	0	3	1	1.5	222	222	
11 to 11.25 minutes	4	II	0.07	0.03	0.12	3.5	0	7.5	0	±4	218	218	
12.5 to 12.75 minutes	4	III	0.06	0.03	0.12	4	0	6	0	±4	218	218	

TABLE 7.—*Results in Experiment 7*

				Electrocardiogram										
				Interval, Second			Amplitude, Millivolt					Rate		
Sept. 10, 1924 Time	Injection	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V	Remarks
10:30 a.m.	.....	1	II	0.06	0.03	0.12	5	3	18	17	4	200-240	200-240	Sinus arrhythmia
		1	II	0.06	0.03	0.12	4.5	4	20	18	4	143-214	143-214	
10:33 a.m.	Atropin, 0.5 mg. intravenously													
10:35 a.m.	.....	2	II	0.05	0.03	0.12	4.5	3	14	15	4	271	271	
10:37 a.m.	Histamin, 16 mg. intravenously													
After injection of histamin														
10:37¼ a.m.	0.25 minute	3	II	0.16	0.03	0.12	4	4	13	16	4	262	133	Partial heart block, 2:1
		3	II	0.06-0.20	0.03	0.12	4.5	4	10	15	4	207	171	Complete auriculoventricular dissociation
		3	II	0.04-0.20	0.03	0.12	3.5	3	9	15	4	245	191	
10:45 a.m.	8 minutes	3	II	0.16	0.03	0.12	3.5	2	8	7	3	257	257	Delayed auriculoventricular conduction
10:48 a.m.	11 minutes	4	II	0.12	0.03	0.12	4	2	8	7	−3	250	250	
10:50 a.m.	12 minutes	4	II	0.08	0.03	0.12	4	2	7	7	4	250	250	

TABLE 8.—*Results in Experiment 8*

Sept. 12, 1924 Time	Injection	Number	Lead	Electrocardiogram: Interval, Second P-R	Q-R S	S-T	Amplitude 10^{-4} Volt P	Q	R	S	T	Rate A	V	Remarks
11:52 a.m.	.....	1	II	0.07	0.03	0.12	5	3	18	4.5	4	207	207	
12:15 p.m.	Atropin, 1 mg.													
12:25 p.m.	Atropin, 1 mg.													
12:26 p.m.	.....	2	II	0.07	0.03	0.12	5	3	16	5	5	205	205	
12:30 p.m.	26 mg. of histamin injected													
After injection of histamin														
12:31 p.m.	1 minute	3	II	?	0.03	0.12	5	3	17	5	6	191	150	Complete auriculoventricular dissociation
12:32 p.m.	2 minutes	3	II	?	0.03	0.12	6	3	18	6	7, 8*	187	164	T or R superimposed by P*
12:33 p.m.	3 minutes	3	II	?	0.03	0.12	5	3	17	5	6, 8*	187	164	
12:34 p.m.	4 minutes	3	II	?	0.03	0.12	5	3	14, 17*	5	6, 8*	200	180	Ventricular arrhythmia
12:35 p.m.	5 minutes	3	II	0.20	0.03	?	7*	3	14	5	8*	191	191	Ventricular rate regular P superimposed on T, both increase in amplitude
12:36 p.m.	6 minutes	3	II	0.16	0.03	?	6*	3	14	5	7*	200	200	
12:37 p.m.	7 minutes	3	II	0.15	0.03	0.12	5.5*	3	13	5	6*	195	195	
12:38 p.m.	8 minutes	3	II	0.13	0.03	0.12	5.5	2.5	13	5	6	200	200	Auriculoventricular conduction delayed
12:40 p.m.	10 minutes	3	II	0.09	0.03	0.12	6	2.5	12	5	6	218	218	

* Figures denote amplitude of superimposed waves.

TABLE 9.—*Results in Experiment 9*

Sept. 19, 1924 Time	Injection	Number	Lead	Electrocardiogram: Interval, Second P-R	Q-R S	S-T	Amplitude 10^{-4} Volt P	Q	R	S	T	Rate A	V	Remarks
10:01 a.m.	.....	1	II	0.08	0.04	?	6	3	16	7.5	?	218	218	
11:05 a.m.	Atropin, 1 mg.													
11:06 a.m.	.....	2	II	0.08	0.04	?	5	3	12	7	?	200	200	
11:11 a.m.	.....	2	II	0.08	0.03	?	3	2	5	3	?	200	200	Slurred R in Lead II
11:14 a.m.	22 mg. of histamin injected													
After injection of histamin														
11:14¼ a.m.	0.25 minutes	3	II	0.13	0.04	?	4.5	2.5	9	3	?	175	175	Delayed auriculoventricular conduction
11:14½ a.m.	0.5 minutes	3	II	?	0.04	0.14	4	2	7	3	—4	171	142	Complete auriculoventricular dissociation
11:15 a.m.	1 minute	3	II	?	0.03	?	?	2	8	3	?	?	140	
11:15½ a.m.	1.5 minutes	3	II	?	0.04	?	4	2.5	8	3	—3	175	158	Ventricular arrhythmia
11:16 a.m.	2 minutes	3	II	?	0.03	?	3	2.5	6, 8*	2	?	179	164	Slurred R
11:16½ a.m.	2.5 minutes	3	II	0.24	0.04	?	3	2	7	3	?	176	176	Delayed auriculoventricular conduction
11:17 a.m.	3 minutes	3	II	0.18	0.03	?	3.5	2.5	7	3	?	176	176	
11:17½ a.m.	3.5 minutes	3	II	0.18	0.04	?	4	2.5	5	3	?	180	180	Notched P in Leads III at 11:16½ a.m. and at 11:19½ a.m.
11:18 a.m.	4 minutes	3	II	0.16	0.04	?	4	2.5	6	3	?	180	180	
11:18½ a.m.	4.5 minutes	3	II	0.15	0.04	?	4	0	6	3	?	176	176	Slurred R in Leads III at 11:16½ a.m. and at 11:17 a.m.
11:19 a.m.	5 minutes	3	II	0.14	0.04	?	4	0	7	3	?	180	180	
11:19½ a.m.	5.5 minutes	3	II	0.13	0.04	?	4	0	7	2.5	?	176	176	

* Figures denote amplitude of superimposed waves.

The electrocardiogram, taken about fifteen seconds after the injection of histamin, showed prolonged P-R intervals and slightly increased amplitude of the P and R waves. Both the auricular and the ventricular rates were equally diminished, neither dissociation nor arrhythmia being shown. From one-half to two minutes after the injection of histamin, a complete auriculoventricular dissociation was indicated by the absence of regular relationship between the P waves and the Q-R-S complexes, the P-R intervals varying considerably. The ventricular complexes occurred at abnormal intervals, that is, every fourth or fifth interval and during the latter stage of this period every sixth or seventh interval was irregularly prolonged, by from 30 to 50 per cent., as compared with the others which were nearly regular, although slightly longer than those of the auricular. From one to one and one-half minutes after the injection of histamin, instead of the P waves there occurred irregular waves, varying in rate, amplitude and contour, which appeared to reveal coarse, auricular fibrillation or impure flutter. More than two and one-half minutes after the injection of histamin, there was a considerable delay in the auriculoventricular conduction, but no dissociation. The heart rate was regular, though still slowed. The P waves were notched at the beginning of the period.

COMMENT

As has been shown in the foregoing electrocardiographic records, intravenous injection of histamin dichlorid, 2 mg. for each kilogram of body weight, causes prompt changes in the auriculoventricular conduction. A delay in the conduction is clearly indicated by the lengthening of the P-R intervals. In twelve normal dogs with intact, as well as divided, vagi, kept under ether or urethan anesthesia, the P-R interval was found to range from 0.06 to 0.11 second, and to average 0.08 second. Within one minute after the injection of histamin, the conduction time, when it could be measured, was lengthened to more than 0.13 second, and in an extreme case, to 0.32 second. In the records taken as early as fifteen seconds after the injection of histamin, the prolongation of the conduction time was already evident. The return to the normal range of the conduction time occurred at the points of from two to thirteen minutes, an average of seven and one-half minutes after the injection. Complete return to the original conduction time was attained at from eight to nineteen minutes (an average of twelve and one-fourth minutes) after the injection. Complete auriculoventricular dissociation, partial heart block or both occurred in each instance following the injection. Three of nine dogs showed periods of both complete and partial heart block; four, complete auriculoventricular dissociation, and two others, only partial heart block. In four cases in which the electrocardiograms were taken as early as fifteen seconds after the injection of histamin, in three the period of partial heart block developed first, and it turned into that of complete auriculoventricular dissociation at from one to one and one-half minutes after the injection. In another case, complete auriculoventricular dissociation began one-half minute after the injection, without a preceding period of partial block. The complete or partial heart block disappeared at the end of the periods

of from one and three-fourths to seven minutes (average four and one-half minutes) after the injection of histamin. Not infrequently, ventricular arrhythmia attended the auriculoventricular dissociation. Sometimes periodic occurrence of partial heart block produced irregular pulse. The impairment of the conduction, as described, seems not to be influenced by the administration of ether, urethan or procain for the purpose of anesthesia (Fig. 4).

Depression of the auriculoventricular conduction of the impulse may be induced by stimulation of the vagi, as has been shown by Mackenzie,[9] and by Robinson and Draper.[10] The depression of the conduction resulting from the administration of digitalis is partially or completely removed by atropin, as reported by Cohn and Fraser,[11] and by White and Sattler.[12] That histamin may stimulate the vagi has been suggested by a number of investigators. According to Barger and Dale, Dale and Laidlaw, and Ackermann,[13] histamin possesses a weak pilocarpin-like action on the glands, which can be completely abolished by atropin. Keeton, Koch and Luckhardt [14] assert that the stimulating effect of histamin on the gastric secretion can be inhibited by atropin, but not completely, if the histamin is given in large doses. So far as I know, however, the disturbance in the auriculoventricular dissociation due to histamin cannot be prevented by the paralyzing of the vagi. In most of the animals in this series, the vagi were divided. To some of them, also, atropin was given in doses more than sufficient to paralyze the vagi completely. According to Pilcher and Sollmann,[15] the dosage of atropin required to paralyze the vagi of dogs completely is between 0.01 and 0.075 mg. for each kilogram of body weight, and its maximal effect lasts for from five to twenty minutes. In the present experiments, from 0.065 to 0.156 mg. of atropin sulphate for each kilogram of body weight was injected intravenously, and the changes

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13. Ackermann, D.: Ueber den bakteriellen Abbau des Histidins, Ztschr. f. physiol. Chem. **65**:504-510, 1910.

14. Keeton, R. W.; Koch, F. C., and Luckhart, A. B.: Gastrin Studies: Response of Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atropin, Am. J. Physiol. **51**:469 (April) 1920.

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in the conduction due to histamin were produced at from four to nine minutes after atropin had been administered. It is evident, therefore, that the disturbances in the auriculoventricular conduction occurring after the injection of histamin are not due to stimulation of the vagus, neither its centers nor its endings.

As Roaf and Sherrington,[16] Lewis, Mathison and Oppenheimer[17] have shown, asphyxia causes profound disturbances in auriculoventricular conduction, the development of which is independent of the central nervous system. According to the results of electrocardiographic investigation by Lewis and his collaborators, the delay in the conduction and the heart block occur regularly within a few minutes of the cessation of respiratory ventilation in the intact curarized animal with or without vagal section, in the decerebrated and the spinal animal, and after atropinization. It is well known that histamin causes promptly severe respiratory difficulties, presumably by strong constriction of bronchioles and pulmonary vessels. Such embarrassment in the functioning of the lung and its circulation may result in acute asphyxia which is capable of inducing heart block, as has been shown. Greene and Gilbert,[18] studying the blood pressure and electrocardiographic changes in dogs during extreme want of oxygen, showed that, in asphyxiation, there occurred inverted or suppressed P waves, partial or complete heart block, sometimes reversed rhythm, and ectopic beats. They noted, however, the complete disappearance of these changes after section of the vagi. Willius[19] obtained electrocardiographic records from dogs, all of whose vessels leading to and from the heart were simultaneously and completely clamped, and demonstrated the occurrence of various types of nodal rhythm, sino-auricular block, delayed auriculoventricular conduction, and complete or partial heart block in this condition. He observed further, that after section of the vagi, an exactly similar procedure was not followed by the appearance of any of the foregoing changes. The disturbance of the heart's action induced by the injection of histamin in the present experiments is decidedly different from those observed by Greene and Willius in asphyxia in that the former still occurs after vagal section or atropinization.

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19. Willius, F. A.: Changes in the Mechanism of the Human Heart Preceding and During Death, M. J. & Record **119**:xlix-liv (March 19) 1924.

There have been various clinical and anatomic observations suggesting that coronary sclerosis may be one of the important etiologic factors of the heart block, and that some ischemia of the auriculoventricular bundle may be responsible for the diminution and its conductivity. According to Dale [20] and his co-workers, histamin, if injected intravenously in a large dose, produces strong constriction of the arteries and oligemia due to retardation of blood flow in relaxed capillaries, and loss of plasma through abnormally permeable capillaries. It seems not unlikely that such vascular disturbance may interfere with the adequate blood supply of the tissues of the heart, and contribute to the development of impaired auriculoventricular conduction. Further investigations are desirable to establish the point whether or not histamin possesses a direct depressor action on the auriculoventricular bundle.

Taylor [21] reported a case of transient heart block due to intestinal toxemia. A similar case was observed by Hirschfelder [22] who asserted that ptomaine poisoning or auto intoxication due to severe gastro-intestinal disturbance may give rise to the heart block. Mellanby [23] suggested that some type of severe gastro-intestinal disturbance with diarrhea and vomiting in children may be due to absorption of histamin or the histamin-like substance formed in the intestinal tract. Gerard [24] suggested that histamin may be responsible for the toxemia in cases of intestinal obstruction. The present investigation adds further evidence that histamin can cause striking disturbances in the auriculoventricular conduction.

SUMMARY

Histamin, if injected intravenously into dogs in a dose of 2 mg. of its dichlorid for each kilogram of body weight, promptly caused a delay in the auriculoventricular conduction, and transient, complete or partial heart block. The average duration of the delayed conduction was approximately twelve minutes following the injection of histamin, and that of heart block four and one-half minutes. The foregoing disturbances in conduction occur even after vagal section or atropinization.

20. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamin and of Some Other Substances, J. Physiol. **52**:110-165 (July) 1918. Dale and Laidlaw (Footnote 5).

21. Taylor, F. L.: A Case of Transient Heart Block Due to Intestinal Toxemia, J. A. M. A. **50**:1246-1247 (April 18) 1908.

22. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 581.

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MEASUREMENT OF THE BODY SURFACE IN MEN AND IN WOMEN *

ROBERT FAILLIE, M.D.
PARIS, FRANCE

Practical determination of the body surface is a question of the highest importance, as indicated by the numerous contributions on the subject. The present discussion deals with a practical method for making such determinations. First, however, it is well to review the work of the physiologists, which is employed by physicians as a basis.

Recent clinical studies of the basal metabolism have confirmed the importance of the law that surface is an important factor in animal thermogenesis.[1] This law, perceived by Bergman,[2] in 1848, was first fully formulated by Rubner,[3] in 1883, following his combustion tests, and by Richet,[4] whose studies of 1884 and 1885 refer to calorimetric measurements. It shows that animal thermogenesis is fundamentally expressed in terms of the cutaneous surface, and not on the volume or weight. Figures obtained by various observers appear in the accompanying table.

Comparative Body Measurements of Different Observers

Observers	Body Weight, Kg.	Gross Calories of the Ration	Calories per Square Meter
Rubner	67	3,094	1,520
Voit and Pettenkofer	70	3,054	1,470
Lapicque and Marette	73	3,027	1,420
Hirschfeld	73	3,318	1,560
Tsuboi and Murato	46	2,355	1,430
Kumagava	48	2,478	1,550

This table shows the practical constancy of heat expenditure per square meter, regardless of variations in body weight. Voit's statement that heat expenditure for animals analogous with respect to this single factor is uniformly equivalent to 1,000 calories per square meter has been clearly proved inexact by M. and L. Lapicque.[5] The latter have

* These results were first reported, Feb. 25, 1924.

* Translated by Theodore C. Merrill, Paris, 10 bis rue Herran.

1. Benedict, F. G., and Talbot, F. B.: Metabolism of Growth from Birth to Puberty, Carnegie Institute Publication, No. 302, 1921.

2. Bergman: Wärmeökonomie der Thiere, Göttingen, 1848.

3. Rubner, M.: Ueber den einfluss der Körpergrösse auf Stoff und Kraftwechsel, Ztschr. f. Biol. **19**:545, 1883.

4. Richet, C.: Mesure des conbustions respiratoires chez le chien, Arch. f. Physiol. **2**:17-30 (Jan.) 1890; Mesures de calorimétrie, Arch. f. Physiol. **6**:237, 450-497 (Aug.-Sept.) 1885.

5. Lapicque, M., and Lapicque, L.: Compt. rend. Soc. de biol. **66**:289 (Feb. 20) 1909; ibid. **66**:528 (March 27) 1909; ibid. **67**:337 (July 31) 1909; ibid. **70**:375 (March 11) 1911; ibid. **70**:737 (May 13) 1911; Bull. Soc. d'hyg. aliment., Nos. 5 and 6, 1911; Bull. du Muséum d'hist. nat., No. 1, 1911, p. 2; Compt. rend. Acad. d. sc., June 13, 1921, p. 1526.

shown the merely approximate nature of the law of surface, in tests made with various animals and at various temperatures. The law is strictly applicable only at a certain external temperature characteristic for each animal species, in which conditions of heat production and heat expenditure required to produce equilibrium are also characteristic. At the specific temperature, the total heat loss due to various physical conditions is equivalent to the heat derived from the basal metabolism. Evidently, then, sweeping application of the surface law to all animal species must produce inexact findings.

Benedict has recently revived Voit's theory that basal heat loss is proportional to the total nitrogen of the organism, rather than to its surface. For normal organisms, the conclusions of Lapicque and of Benedict may perhaps be harmonized by a relation possibly existing between the cutaneous surface and the protoplasmic mass of the body. Apart from such restrictions, however, surface is undoubtedly the fundamental element permitting scientific estimation of the basal metabolism, or work, as proved by comparison with results derived from analyses of the respiratory gases. While analytic methods of this kind have been highly perfected, methods and formulas for estimating the body surface are yet debatable, because direct measurements involve much labor and difficulty, and have been rarely made. The various empiric formulas available differ considerably.

Direct measurements of the body surface have utilized three main methods. The first, employing geometric figures traced on the skin, was used by Meeh,[6] Fubini and Ronchi,[7] Bouchard,[8] Letulle and Pompilian,[9] and Lassablière.[10] In the second process, the body surface is calculated by finding the total area of paper, tin foil or similar material required to cover the surface of the body, or by weighing the material so employed. Funke [11] adopted this method for the first time, sticking squares of paper of known area on the skin of a cadaver. Lissauer,[12] Variot and Saint Albin,[13] the Du Bois [14] brothers and others have

6. Meeh: Oberflächenmässungen des menschlingen Körpers, Ztschr. f. Biol. **15**:425, 1879.

7. Fubini and Ronchi: Ueber die perspiration der CO_2 beim Menschen, Moleschotts Untersuchungen, 3, Naturlehre, 1881.

8. Bouchard: Compt. rend. Acad. d. sc., 1897, p. 845; Traité de pathologie générale, Paris, **3**:200-384, 1900.

9. Letulle and Pompilian: Bull. Soc. d'hyg. aliment., 1906, p. 708.

10. Lassablière: Compt. rend. Soc. de biol., 1910, p. 339.

11. Funke: Moleschotts Unters, 2, Naturlehre **4**:36, 1858.

12. Lissauer: Oberflächenmässungen an Saüglingen und ihre Bedeutung für Nahrungbedarf, Jahrb. f. Kinderh., 1902, p. 392.

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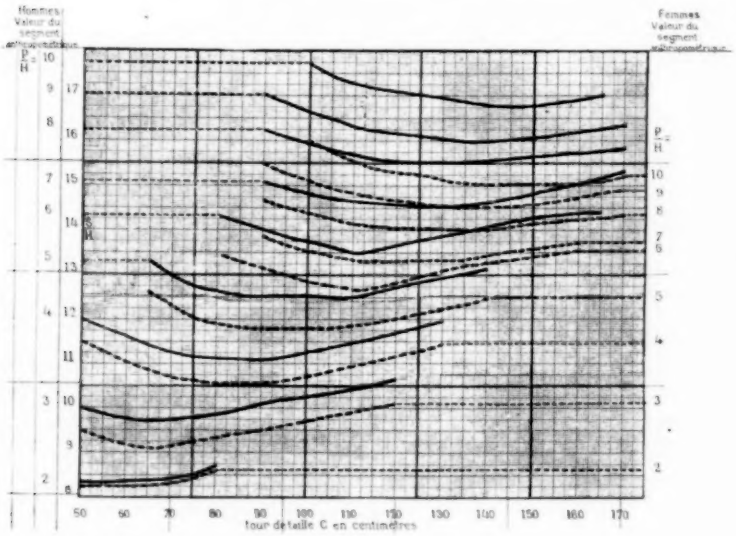
14. Du Bois, D., and Du Bois, E.: The Surface of the Body, Arch. Int. Med. **17**:863 (June) 1916.

employed it. The third process, in which the surface of adhesive bandages applied to the body is estimated, has been chiefly employed by Bergonié and Sigalas.

Other ingenious methods have been devised. Roussy traces figures on the skin, measuring them by means of two small rollers placed at the ends of an axle bearing a revolution counter. The number of revolutions made by the rollers is supposedly proportional to the surface over which they travel. This method is fairly exact. D'Arsonval converts his subject into a Leyden jar, measuring the quantity of electricity



Abacus for measuring the human body.

required to charge the body surface. Utilizing measurements made in six adults and ten children, Meeh has established an empiric formula based on the mathematical relation according to which the surfaces of similar solids are proportional to their volumes as raised to the two-thirds power, or the cube root of the square of the volumes concerned. In this case, volume is represented by weight. By this method, Meeh determined the constant 12.312, applicable to adults, and another constant, 11.9, for use with children. These constants multiplied by the cube root of the square of the body weight should supply the body surface. When compared with direct measurements, Meeh's method proves to involve error sometimes reaching 33 per cent.

Minute review of all the studies made on the subject is scarcely necessary. The conception and technic originated by Bouchard, however, are fundamental and merit special attention. His critical discussions show the large error produced when body weight constitutes the sole criterion, such error maximally reaching 33 per cent. Bouchard also shows that estimates based only on height and weight may cause error of 15 per cent., and proves still further that the error is very small with formulas utilizing the fundamental constant constituted by the anthropometric segment in association with the girth, or circumferential measurement as made at the level of the umbilicus by tailors. The anthropometric segment consists of the ratio of the weight, expressed in kilograms, to the height, expressed in decimeters. It is thus equivalent to the average weight per decimeter of the subject's height.

The discussion and conclusions contained within the present paper are based on some eighty measurements made directly on persons varying greatly in size. The method employed was the laborious but exact one of triangulation. Bouchard's successors seem very imperfectly acquainted with his masterly work, the Du Bois brothers and their followers accepting formulas which Bouchard has proved incorrect by actual figures. The Du Bois brothers base their weight-height formula on five direct measurements and on certain hypothetic estimates. They assert that Bouchard's methods are unduly complicated. It is intended here to show that Bouchard's formulas may be readily utilized in the construction of an abacus, or graph, that is very simple and practical.

Bouchard's [15] formulas for men and women, as indicated by Broca,[16] may be expressed in the form

$$S = A\,C\,H + B\,\frac{P}{C} + D\,H\sqrt[2]{\frac{P}{3.14\,H}}$$

In this equation, A, B and D are constants. C represents the girth, or circumferential measurement of the abdomen, expressed in centimeters; H, the height in decimeters, and P, the weight in kilograms. If the foregoing equation is simplified by dividing its terms by H, its equivalent is the following:

$$\frac{S}{H} = a\,C + b\,\frac{1}{C} + d$$

a, b and d are values expressing the ratio of the weight to the height. In other words, they solely represent functions of the relation $\frac{\text{Weight}}{\text{Height}}$. The proportion $\frac{S}{H}$ represents the surface of the anthropometric segment. The values of a, b and d, deducible from Bouchard's formulas, are graphically indicated by Broca.[16]

15. Bouchard: Compt. rend. Acad. d. sc. **124**:848 (April 20) 1897.
16. Broca, André: Précis de physique médicale, pp. 47 and 48.

The abacus, or graph, here presented has been constructed from the values thus shown in the foregoing. Its curves, or tracings, show the surface of the anthropometric segment, or $\frac{\text{Weight}}{\text{Height}}$ relation, as employed in connection with the girth, *C*. For utilizing the graph, the weight-height ratio $\frac{\text{Weight}}{\text{Height}}$ must be ascertained, weight being expressed in kilograms and height in decimeters. The girth, *C*, is stated in centimeters. Its value in the given case is sought on the abscissa. At the point corresponding to this value, a perpendicular is erected and continued upward until it meets the curve corresponding to the given $\frac{\text{Weight}}{\text{Height}}$ ratio. This point of intersection, projected on the ordinate for men or for women, as the case may be, gives a reading which expresses the $\frac{\text{Surface}}{\text{Height}}$ ratio, or surface of the anthropometric segment. The surface, *S*, is then easily calculated by multiplying the quotient representing the ratio by the given height. This total surface is stated in square decimeters.

The graph may be used easily and rapidly. It is hoped that it may supply exactness for estimating metabolism, and without being more complicated than the less accurate devices of the kind already existing. The curves are particularly interesting because they show that anthropometric segments possess minimal circumferences. If the circumference diminish, the surface increases and the ratio $\frac{\text{Weight}}{\text{Height}}$ is maintained only through compensation afforded by increased development of the limbs, or by some malformation. If the circumference increase, the anthropometric segment represents that one corresponding to a lesser body height, the condition present being one of obesity. Since the minimal surface corresponds to the minimal basal metabolism, or condition fundamental for providing the maximal output of energy, a physiologic relation, or canon, exists between the girth, or abdominal circumference, and the anthropometric segment. This physiologic canon suggests, and may be interestingly compared with, the esthetic canon of proportions devised by Leonardo da Vinci for the correct pictorial or sculptural representation of the human figure.

The flattening of the curves in the graph shows that the physiologic limits are somewhat elastic for moderate anthropometric segments. For small segments weighing less than 2 kg. per segment, physiologic conditions cease to exist, the subject presenting a marasmic state. For segments weighing 6 kg. each, a limit beyond which the subject becomes obese, the corresponding physiologic girth is 110 cm. In other words, the canon is normal and physiologic under these conditions. Above and below the circumference of 110 cm., surface increases rapidly, and obesity appears. With anthropometric segments heavier than 6 kg. each, the physiologic canon is annihilated, obesity exists, and the conditions present are pathologic.

For terminating this paper, nothing could be more appropriate than the expression made use of by Bouchard in closing his work on general pathology:

> The exposition of all this has been much prolonged. Still more time has been required for conceiving and executing it. The object of so much time and trouble has been to save time and trouble for those who wish to undertake such studies. The result may perhaps be identical with the object.

BLOOD VOLUME

II. A COMPARISON BETWEEN TOTAL BLOOD VOLUMES DETERMINED BY PLASMA VOLUME METHODS AND BY A NEW CORPUSCLE VOLUME METHOD *

WINIFRED ASHBY, PH.D.
ROCHESTER, MINN.

The method of measuring total blood volume by determining the degree of dilution of the transfused corpuscles among the corpuscles of the recipient, previously described,[1] has been applied to cases of secondary anemia, primary anemia, and hemorrhage resulting from operation; the results obtained are compared with the data already on record derived by the use of vital red in similar groups of cases. Since, as has been shown, this method is based on a determination of corpuscle content, a comparison of the results obtained by it with those obtained by a method in which the whole blood volume is calculated from a determined plasma volume is of interest because of its bearing on the problem of the uniformity of distribution of the red corpuscles in the circulation.

The means of measuring plasma volume are numerous. The most satisfactory is the injection of a substance, soluble in the plasma, and the subsequent determination of its degree of dilution. Among the substances used for injection are tetanus antitoxin, gum acacia, hemoglobin and various dyes, but the only considerable amount of clinical data on blood volume has been collected by the use of the dye method, introduced by Keith, Rowntree and Geraghty.[2] The results obtained by the various methods are, in general, in agreement. There are only two methods for measuring the corpuscle volume of the blood, aside from that introduced in this study. One of these involves the death of the animal, and consists of bleeding and washing out the hemoglobin; this is open to the objection that all the hemoglobin may not be removed. The other, which consists of the measurement of the degree of dilution of carbon monoxid in the hemoglobin contained in the body, is open to the objection that the hemoglobin in the muscles may also take part

* From the Mayo Foundation.

1. Ashby, Winifred: Blood Volume, I, A Method for Determining Whole Blood Volume, Based on the Circulating Corpuscle Volume, Arch. Int. Med.

2. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547-576 (Oct.) 1915.

in the dilution of the known amount of carbon monoxid resulting in too high an estimate for the blood corpuscle content. Both methods, however, on calculation of the whole blood volume from the corpuscle volume, give lower values (7 per cent.) than are obtained by a calculation of the whole blood volume from the plasma volume.

The greater blood volumes obtained by the determination of plasma volume have been explained on the basis of appreciable loss of the injected substance, soluble in the plasma, before complete mixing has taken place. Lamson and Rosenthal,[3] who have studied the initial changes which take place in the dilution of vital red after injection, find irregularities which, on the assumption of a constant volume during the time of examination, they attribute to irregularities in the relative degree of mixing and rate of disappearance from the circulation, and consider that there is indication that mixing is not complete before appreciable elimination takes place. Whipple,[4] on the other hand, with much reason, calls attention to the wide range in the physical and chemical properties of the substances used for the test, and the similarity of the results obtained with them, arguing that if there were an appreciable loss before complete mixing took place, it should be markedly different with these very dissimilar substances, and should cause a greater difference in results. Whipple [4] considers that the methods of measuring plasma volume give correct results, as does the measurement of corpuscle volume by carbon monoxid, and that the discrepancy between the whole blood volumes calculated from each is due to an uneven distribution in the corpuscles during the course of their circulation, with the result that the hematocrit reading of a sample of blood taken from the vein fails to give an average relationship between corpuscle and plasma. To meet the condition which the relative findings of the two methods would necessitate, a larger proportion of corpuscles must be present in the vessels from which the blood specimens for the hematocrit readings are taken than elsewhere. Whipple offers the suggestion that this relationship is brought about by the presence of a larger proportion of "clear space" as the blood passes into the smaller vessels and capillaries. Krogh,[5] however, as a result of direct observation of blood in the process of flow through the capillaries, does not consider that this would be a factor. As a matter of fact, counts made on the blood taken from the

3. Lamson, P. D., and Rosenthal, S. M.: The Inadequacy of Our Present Blood Volume Methods, Am. J. Physiol. **63**:358-367 (Jan.) 1923.

4. Arnold, H. R.; Carrier, E. B.; Smith, H. P., and Whipple, G. H.: Blood Volume Studies, V, The Carbon Monoxid Method: Its Accuracy and Limitations, Am. J. Physiol. **56**:313-360 (June) 1921.

5. Krogh, August: The Anatomy and Physiology of the Capillaries, New Haven, Yale University Press, 1922.

ear, simultaneously with that from the basilar vein, will be found to be equal, or the count of the blood from the ear will be greater. Since the blood from the ear is derived largely from small vessels and capillaries, this finding does not support the explanation of the discrepancy between the two methods. The work of Scott [6] also argues in favor of an evenness of distribution of the corpuscles in the circulation.

The method for determining blood volume described in the first article of this series [1] consists of the injection of unlike group corpuscles by transfusion, and their subsequent separation from the recipient's corpuscles by means of a serum which agglutinates the recipient's corpuscles. With data on the number of corpuscles injected, the degree of dilution may be determined. Assuming that the transfused corpuscles mix evenly with the native corpuscles and follow the distribution of the latter, the method is based on corpuscle content. Therefore, if there should be any irregularity in the distribution of the corpuscles in the circulation, the error, by this method, should be in the opposite direction to that which would occur with a method based on plasma volume determination. Although the method is technically not highly accurate, it has the advantage, because of the great stability of the unlike group corpuscles, of being free from any question as to whether mixing is complete before appreciable elimination takes place. It is also free from the error which is intrinsic to the carbon monoxid method, owing to the presence of the hemoglobin containing tissues outside the circulation.

The technic described [1] has been followed, except that determinations have been made from blood taken from an ear puncture instead of from a venipuncture. The greater part of the data given here was collected incidentally to a study of the rate of destruction of transfused blood; the advisability of using blood from the vein was not at the time recognized. As the error due to using blood from the ear would be in the direction of too high a count, it will, when it occurs, have caused too small a blood volume. It has apparently not been a factor of any importance as the volumes obtained have proved to be large as compared with results obtained with the carbon monoxid method. At the time when the greater part of this work was done, vital red was not available, and a simultaneous use of other methods was not feasible. Except for two simultaneous tests, the comparison of the results obtained by this method and by the method which measures the plasma volume and calculates the whole volume from it, depends on a comparison of the results obtained in similar groups of cases.

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6. Scott, F. H.: Interchange of Fluid in Blood and Tissue Spaces, Am. J. Physiol. **44**:298 (Oct.) 1917.

In Table 1 are given the results of blood volume determinations by my method in a series of cases of anemia other than pernicious anemia. The results are given in terms of cubic centimeters for each kilogram of body weight on the day of transfusion, and also a few days later, when a readjustment after the transfusion may have taken place. The amount of blood transfused for each kilogram of body weight also is given. In seven cases, between 80 and 85 c.c. for each kilogram of body weight was found. These volumes were usually maintained after transfusion. The volumes are equivalent to the lower volumes found in normal subjects by the vital red method, and reported by Keith,

TABLE 1.—*Blood Volume of Patients with Secondary Anemia After a Single Transfusion*

Case	Age	Sex*	Red Cell Count	Blood, C.c. for Each Kilogram of Body Weight	Blood, C.c. Transfused for Each Kilogram of Body Weight	Days After Transfusion	Diagnosis
9	33	♀	3.96	96	11	0	Pelvic tumor (second transfusion)
18	35	♀	....	84	9	0	Septic teeth, tonsillitis
27	46	♀	3.63	62	6	0	Ovarian tumor (obese)
				52	..	4	
30	27	♀	3.19	81	4	1	Splenic anemia
				81	..	6	
53	39	♀	4.47	81	9	0	Exophthalmic goiter, color index 0.4
				85	..	4	
66	62	♂	3.46	80	6	0	Banti's disease with ascites
99	17	♀	4.73	104	11	1	Malaria
				104	..	28	
101	..	♀	3.46	58	8	1	Uterine fibromas, constant bleeding
117	..	♂	1.99	85	6	0	Transfusion ten days after posterior gastro-enterostomy
				82	..	3	
118	13	♂	1.85	104	14	0	Hemolytic jaundice
65	11	♂	1.99	98	13	0	Lymphatic leukemia
				140	..	3	
				135	..	9	
39	55	♂	3.12	81	7	0	Myelogenous leukemia
115	33	♀	5.13	57†	..	0	Secondary anemia, septic, not rational

* In this table, ♂ indicates male, ♀ female.
† Low volume maintained.

Rowntree and Geraghty. From calculations based on the actual blood volume, the change in the red cell count resulting from transfusion, and the number of corpuscles transfused, which data will be given later,[7] it appeared that, in many cases, a greater increase in volume occurred than could be accounted for by the amount of blood transfused. It would seem probable that, in cases of secondary anemia, transfusion tends to establish a normal blood volume. In a case of malaria and in one in which the patient had received a previous transfusion, the higher volumes of 104 and 96 c.c. for each kilogram of body weight were found. Tests on two children gave values of 104 and 98, which adjusted

7. Ashby, Winifred: Blood Volume, III, Apparent Changes in Blood Volume Induced by Transfusion, and Their Bearing on Methods of Determining Blood Volume by Means of the Degree of Change in a Constituent of the Blood, Following Transfusion of a Known Amount of That Constituent, Arch. Int. Med. **35**:641 (May) 1925.

to 140 c.c. for each kilogram of body weight. Low values of 62, adjusting after four days to 52, and of 58 and 57 were found in a very obese woman, a woman with constantly bleeding fibroids, and in a woman with septic anemia who was irrational.

On the whole, these figures for blood volume are definitely of the same order as those obtained with vital red, by the use of which a comparatively large number of determinations have been made on a similar group of cases. In the series of Keith, Rowntree and Geraghty, a miscellaneous group, five of which showed a reduced cell count, gave the

TABLE 2.—*Blood Volumes of Patients Receiving Transfusions for Primary Anemia*

Case	Age	Sex*	Weight in Kilograms	Red Cell Count	Blood, C.c. for Each Kilogram of Body Weight	Blood, C.c. Transfused for Each Kilogram of Body Weight	Days After Transfusion	Number of Previous Transfusions in Series
20	53	♂	88.2	....	62	4	0	0
					62	...	3	
23	55	♂	66.6	1.23	71	6	0	0
				1.09	71	...	4	
36	42	♂	70.5	....	72	7	1	0
43	49	♂	73.6	1.95	62	5	1	0
45	44	♂	68.2	1.39	60	7	2	0
54	44	♂	66.0	....	69	8	0	0
				1.59	69	...	3	
57	63	♂	71.3	1.54	55	7	0	0
				1.55	52	...	2	
59	52	♀	67.7 (obese)	1.88	49	7	0	0
				2.03	39	...	4	
60	36	♂	61.0	2.46	68	8	0	1
				2.40	71	...	4	
61	42	♂	66.1	1.70	56	7	0	0
				1.77	61	...	1	
68	36	♀	37.3	2.13	78	13	0	...
				1.60	65	...	3	
70	62	♂	54.4	1.02	54	9	0	0
				1.28	73	...	1	
94	55	♂	76.0	2.40	91	6	0	2
				2.38	66	...	4	
97	42	♂	70.5	1.89	75	6	0	0
				2.19	98	...	1	
112	63	♂	63.0	....	87	6	0	4
				2.29	73	...	6	
				2.57	84	...	8	
210	51	♀	45.4	3.06	75	11	1	0
				3.19	77	...	5	
43	49	♂	69.1	2.39	85	6	0	2

* In this table, ♂ indicates male, ♀ female.

following volumes: 93, 88, 84, 80, 92, 84, 114, 96, 96 and 91. In two cases of extreme secondary anemia, in which the red cell counts were 1,070,000 and 1,500,000, respectively, the blood volume for each kilogram of body weight was 73 and 75 c.c., while, in a case of malnutrition, it was 74. In a more recent series, Keith [8] has reported a volume of 67 c.c. for each kilogram of body weight, and Bock [9] reports, for seven miscellaneous cases with an average cell count of 3,900,000, an average

8. Keith, N. M.: The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am. J. M. Sc. **165**:174-184 (Feb.) 1923.

9. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83-101 (Jan.) 1921.

volume of 71 c.c. for each kilogram of body weight. In three cases of leukemia, Keith [8] finds values varying from 96 to 131, 100 to 123, 87 to 102, and, in a case of Banti's disease, a volume of 98 c.c. for each kilogram of body weight was found.

Blood volumes in seventeen cases of pernicious anemia are given in Table 2. Most of the patients received a series of three or more transfusions of 500 c.c. each, at intervals of about a week. Some of the patients received transfusions for the first time; others had had a previous series of transfusions. The average volume of twelve patients who received either their first transfusion, or the first of the present

TABLE 3.—*Blood Volumes Found After Postoperative Transfusions*

Case	Age	Sex*	Red Cell Count	Days After Operation	Transfusion	Blood, C.c. for Each Kilogram of Body Weight	Operation
22	32	♂	....	4	4	85	Posterior gastro-enterostomy
				11	11	92	
			4.30	22	22	88	
38	32	♀	2.96	6	5	44	Removal of multiple lipoma; Von Recklinghausen's disease; moderately obese
			2.92	10	9	46	
			3.67	21	20	50	
			3.07	24	23	57	
			3.75	27	26	62	
			4.00	30	29	72	
			4.29	33	32	70	
			4.11	35	34	68	
50	50	♂	4.40	19	12	81	Choledochostomy and cholecystectomy
			4.50	27	20	98	
			4.67	29	22	88	
				31	24	90	
63	33	♂	4.98	0	0	39	Nephrectomy
			3.12	2	2	66	
			4.42	30	30	91	
84	46	♀	3.45	0	0	29	Carcinoma of the kidney; nephrectomy; obese
			2.83	1	1	36	
			3.72	8	8	88	
			4.20	12	12	82	
114	..	♀	3.63	4	4	45	
			3.49	6	6	52	
			3.14	11	11	76	
			3.47	15	15	81	

* In this table, ♂ indicates male, ♀ female.

series, was 65.8; the average red cell count was 1.84. Bock, in a series of seven patients with pernicious anemia, found an average volume of 57 (extremes of 43 to 73), but as the average cell count of these patients was 1.6, they were evidently in a poorer condition than those of the group tested by my method. Keith [8] has reported the blood volume of a series of thirteen patients on some of whom multiple determinations were made. The average of the first volume determinations made on each patient is 79.8 c.c. for each kilogram of body weight, and of the corresponding red cell counts, 1.76. These values for blood volume are higher than those found, in my series, for the first transfusion; the patients were presumably under treatment, while my figure of 65.8 was obtained from patients at the beginning of treatment. In four cases

cited in Table 2, in which the unlike group transfusion from which the blood volume determination was made was not the first in the series, the blood volume for each kilogram of body weight was 63, 95, 96 and 85 c.c. Taking into consideration the probable difference in the condition of the patients, the figures for blood volume in my series of patients with pernicious anemia would seem to agree very well with those found by Keith and Bock with the use of vital red.

In the eight cases on record in which the carbon monoxid method was used to determine blood volume in patients with pernicious anemia, the range as determined by Smith,[4] 47 to 117, also is comparable to that found by the vital red method. In cases of pernicious anemia, there is apparently not the discrepancy between the method of estimating blood volume by determining the serum volume and the method of estimating it from a determination of the corpuscle volume by the carbon monoxid method which appears in normal cases.

In Table 3 are given blood volume changes which have been found on recovery from operation with hemorrhage, requiring transfusion. Comparable series are given by Keith [10] and by Robertson and Bock,[11] in their studies of wounded soldiers. These data on the blood volume are somewhat inaccurate, as the transfusions were given in emergency, but are reasonably reliable.

The blood volumes finally established are comparable to those found by the vital red method for normal subjects, and for the recovered soldiers of Keith, following intravenous treatment. The progress of the establishment is also similar to that found by Keith. The blood volume of the moderately obese patient with Von Recklinghausen's disease did not return to normal, although the patient recovered satisfactorily. This may have been due to a peculiarity of the patient, or to an inadequate estimate of the number of corpuscles transfused. The very low blood volume of 39, found in Case 33, and of 29, found in the case of the obese woman, would seem lower than is probable. As the blood specimens from which the blood volume determinations were made were taken from the ear, it is likely, in view of the great discrepancy between the ear and vein count found by Cannon [12] in shock, that these counts were unduly high, and consequently gave too low a blood volume reading, although Lee [13] reports as low as 30 per cent. normal blood volume in wound shock.

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10. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, 1919, Special Report No. 27.

11. Robertson, O. H., and Bock, A. V.: Blood Volume in Wounded Soldiers, J. Exper. Med. **29**:155 (Feb.) 1919.

12. Cannon, W. B.; Fraser, J., and Hooper, A. N.: Some Alterations in Distribution and Character of Blood in Shock and Hemorrhage, J. A. M. A. **70**:526-531 (Feb. 23) 1918.

13. Lee, R. I.: Field Observations on Blood Volume in Wound Hemorrhage and Shock, Am. J. M. Sc. **158**:570-576 (Oct.) 1919.

Simultaneous tests were made by my method and by the vital red method on a patient with pernicious anemia, five days after transfusion had been given. The determination was made from blood taken from the vein. In this instance, the counts of blood specimens taken from the vein and from the ear were equal. The volume for the whole blood by the vital red method was 78.8; by my method, 77. Of course no great importance can be attached to the close agreement of this single set of parallel determinations; the main evidence lies in the general agreement between blood volumes found by my method and those found by the use of vital red in the same type of case.

Simultaneous tests made on a patient with lymphatic leukemia, having a high white count, 445,000, did not give equal results. The volume by my method was 66, while by the vital red method, it was 87.9. The white cells, which are unagglutinable, were distinguished by staining the preparation with brilliant cresyl blue. Many of the white cells, however, did not stain sufficiently to make them easily distinguishable from the red cells, and it is probable that many of them were counted as reds, resulting in too high a count and too low a blood volume. The white counts in the two cases of leukemia, quoted in Table 1, were not high enough to be considered a factor.

Tables 1 and 2 include all cases of secondary anemia and primary anemia on which complete data for determining the blood volume were available; that is to say, in which it was possible to get satisfactorily checking and duplicate counts of the unagglutinable corpuscles in the patient's blood before and after transfusion, and of the blood transfused, and in which I had an accurate record of the amount of blood given. There were, however, many other cases in which all these data were not complete, but in which a fairly reliable estimate could be made. The volume estimates for these cases agree with those given.

SUMMARY

Total blood volumes estimated by a new method, based on the measurement of the corpuscle content of the circulation following transfusion with blood of an unlike group, are compared with those estimated from plasma volume determinations. By the new method, the transfused corpuscles, after becoming uniformly mixed with the native corpuscles, would follow the distribution of the latter, and any error in the estimation of the total blood volume, owing to an irregularity in the distribution of the corpuscles in the circulation, would be in an opposite direction to the error possible by the plasma volume method, as in any given specimen of blood that was not representative the relative plasma content and corpuscle content, which respectively determine the whole blood volume estimate by each method, would have errors that would vary inversely.

The values for whole blood obtained by the new method are in agreement with those obtained by the vital red method, and in disagreement with the whole blood volumes of normal subjects obtained by the carbon monoxid method. The agreement of the results obtained by these two methods would argue against any irregularity in the distribution of the blood corpuscles in the system, and would suggest that there is some factor inherent in the carbon monoxid method which has caused the low results obtained in normal subjects.

The agreement of the data obtained by the new method, in which there is apparently no question of loss of the injected substance, the dilution of which is to be tested during the time necessary for complete mixing in the circulation, with the data obtained by the method involving the injection of a dye, which is comparatively rapidly eliminated, would indicate that the technic of the dye methods involves no appreciable loss before mixing is complete.

BLOOD VOLUME

III. APPARENT CHANGES IN BLOOD VOLUME INDUCED BY TRANSFUSION, AND THEIR BEARING ON METHODS OF DETERMINING BLOOD VOLUME BY MEANS OF THE DEGREE OF CHANGE IN A CONSTITUENT OF THE BLOOD, FOLLOWING TRANSFUSION OF A KNOWN AMOUNT OF THAT CONSTITUENT *

WINIFRED ASHBY, PH.D.
ROCHESTER, MINN.

During the course of a study of the immediate effect of transfusion on the blood count, certain data have appeared which seem to indicate that, besides the change in volume due directly to the transfusion, changes in the total volume occur, due to increase or decrease in the recipient's plasma. These apparent changes in the blood volume may take place within a short time after transfusion without inconvenience to the patient, and may be either increases or decreases. In certain patients, these changes do not occur, especially in those whose blood is comparatively normal. If they really are blood volume changes, they would be a source of error to any method of determining blood volume, which is dependent on the injection of a known amount of some constituent already present in the blood, and the subsequent measurement of the increase in that constituent, because they would vitiate the initial reading.

Although there is a tendency for blood volume to be constant, this is due to the mobility of the blood volume rather than to its rigidity. The rapidity with which the blood plasma in healthy animals increases, to compensate for loss of blood, is a point of evidence, as also is the tendency for the blood to recover its original volume after transfusion, as has been reported by Keith, who has, in certain instances, found that blood volume was no more increased after transfusion than before. The mobility of the blood volume in response to change in conditions produced by external factors has recently been demonstrated in studies by Barbour [1] on the effect of heat and cold, and possibly also by the rather wide diurnal variation in the hemoglobin content, described by Dreyer.[2]

Although the mechanism of blood volume control is by no means fully understood, Krogh's conception of it would seem to offer a good

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* From the Mayo Foundation.

1. Barbour, H. G.: Heat Regulation and Water Exchange, I, Effects of Hot and Cold Baths Upon Blood Concentration and Brain Volume Regulation in Dogs, Am. J. Physiol. **67**:366-377 (Jan.) 1924.

2. Dreyer, G.; Bazett, H. C., and Pierce, H. F.: Diurnal Variations in the Hemoglobin Content of the Blood, Lancet **2**:588-591 (Sept. 18) 1920.

working hypothesis: The point of exchange of fluids is the capillary wall, which is permeable to water and to crystalloids,[3] but generally not to colloids. Since crystalloids readily pass through the capillary walls, they have no permanent part in the maintenance of blood volume. This function is performed by the slight osmotic pressure of the colloids. The capillaries of the intestinal tract Krogh regards as being more permeable than those of the rest of the body, and as the location where colloids in a finer state of subdivision are lost. Krogh has correlated the height of an animal with the degree of dispersion of the colloids of its blood, and the consequent osmotic pressure which they are capable of exerting. He finds that the blood serum of a horse, for instance, which, because of the height of the column of fluid in its vessels, is exposed to a higher filtration pressure than that of the rabbit, not only contains more serum protein than that of the rabbit, but its serum proteins are in a finer state of division. Blood volume, then, would be influenced by the state of subdivision of the colloids of the blood, as well as by their amount. A minimal amount of work has been done on the quantitative protein content of the blood serum in normal and pathologic conditions, but our knowledge of its physical state is practically nil.

It would seem quite possible for two human blood serums to exert considerably different osmotic pressures. This would seem especially probable if one serum were derived from a subject in a state of health, and the other from one who was in need of a blood transfusion. The latter serum might not only have a different quantitative content of protein, but also a different qualitative content. It is probable that the ratio between serum globulin and serum albumin would be different in the two bloods, and it is possible that the state of aggregation of the particles of a single constituent might be different. Accordingly, the added serum might exert either greater or less osmotic pressure than the serum of the recipient, in which event it would upset the balance between the tissue fluids and the blood, and cause an exchange of water and salts. It also is conceivable that the added serum might, because of higher or lower alkalinity or other factors, produce a change in the recipient's serum proteins, thus causing a change in their osmotic pressure, and a consequent exchange of fluid with the tissues.

I believe it is probable that some such mechanism will explain the data which follow, although it must be admitted that other explanations than that of change of volume are possible. After a transfusion of unlike blood has been given and the necessary data obtained for deter-

3. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven, Yale University Press, 1922.

mining the blood volume, it has often been noted that either the blood count of the recipient was not raised, even though it had originally been considerably lower than that of the blood transfused, or it was not raised sufficiently to account for the even distribution of all the transfused corpuscles through the circulation of the recipient. On the other hand, the blood count has sometimes been raised too much to account for the amount of blood given. The low count following transfusion is explicable, either on the basis of an exchange of fluid from the tissues to the blood serum, or by an immediate destruction of some of the recipient's own corpuscles. The high count may be explained either by an immediate destruction of some of the transfused corpuscles, giving a higher blood volume estimate than is correct, or by a loss of fluid from blood serum to tissues. The exchange of fluid seems to me the more probable explanation.

Counts were taken before and after transfusion, usually soon after the patient had been returned to his room. The volume of the blood after transfusion was calculated by the method already given; and from the blood volume, the patient's blood count after transfusion, and the amount and count of the transfused blood, a value for the count of the patient's blood before transfusion was calculated; on the basis of a comparison of this calculated count, and the actual count before transfusion, an estimate of the change in blood volume, aside from that due to fluid added by the transfusion, was made. The method of calculation was as follows: the number of corpuscles added by the transfusion, $C_t \times V_t$, C_t and V_t being the count and volume of the transfused blood, divided by V, the patient's blood volume after transfusion, gives the number of corpuscles for each cubic millimeter added by the transfusion. This subtracted from C, the count of the recipient's blood after transfusion, gives the count of the recipient's corpuscles at the volume of the blood after transfusion. This multiplied by $\frac{V}{V - V_t}$ should give the count before transfusion, provided no destruction of corpuscles nor change in fluid content other than that made by the transfusion has taken place. On the assumption that any difference in the observed and calculated count is due to an exchange of fluid between tissue and serum, the original blood volume is obtained from the formula, $V^o = (V - V_t) \times \frac{C^e}{C^b}$, in which C^e and C^b are the calculated and actual blood counts before transfusion. $(V - V_t) - V^o$ will be the change due to exchange of fluid. From these formulas, the apparent changes auxiliary to the transfusion have been calculated in a series of patients with secondary and primary anemia (Tables 1 and 2).

Of the cases of secondary anemia (Table 1), in three there was no change in the count that could be attributed to change in volume that was not accounted for by the transfusion. In two there was a slight increase, and in three an increase in volume beyond that added by the

TABLE 1.—*Immediate Blood Volume Readjustments Apparently Produced by Transfusion in Patients with Secondary Anemia*

	Red Cell Count					Blood Volume					
	Before Transfusion										
Case	Actual	Estimated	After Transfusion	Days After Transfusion	Previous Transfusions	After Transfusion	C.c. for Each Kilogram of Body Weight	Calculated Volume Before Transfusion	C.c. for Each Kilogram of Body Weight	Amount Transfused, C.c.	Change*
9	4.05	4.07	3.96	0	0	4,340	96	3,840	85	500	0
196	3.17	3.43	3.76	0	...	1,035	82	830	65	275	−60
53	4.59	4.50	4.47	0	0	4,250	81	3,750	72	500	0
				5	...	.....	85				
118	1.56	1.42	1.85	0	0	3,430	105	2,700	82	440	200
283	4.82	4.48	4.54	0	2	3,000	67	2,850	53	540	210
66	3.58	3.36	3.46	0	0	6,000	80	5,220	70	420	350
117	1.98	1.74	1.99	0	0	3,820	85	3,120	69	280	420
			2.18	5	...	.....	76				
27	4.00	3.63	3.54	0	0	3,925	61	3,480	49	425	445
			4.21	5	...	.....	52				

* Unaccounted for by transfusion.

TABLE 2.—*Immediate Blood Volume Readjustments Produced by Transfusion in Patients with Primary Anemia*

	Red Cell Count					Blood Volume					
	Before Transfusion										Change Unaccounted for by Transfusion
Case	Actual	Estimated	After Transfusion	Days After Transfusion	Previous Transfusions	After Transfusion	C.c. for Each Kilogram of Body Weight	Estimated Original Volume	C.c. for Each Kilogram of Body Weight	Amount Transfused, C.c.	
57	1.17	1.15	1.54	0	0	3,900	55	3,450	48	450	0
			1.65	6	...	.....	55				
59	1.33	1.43	1.88	0	0	3,300	48	3,040	45	475	−215
			1.77	1	...	.....	45				
61	1.48	1.23	1.70	0	0	3,700	56	2,660	40	500	+560
				6	...	.....	62				
97	1.90	1.59	1.89	0	0	5,350	75	4,100	58	440	+810
			2.19	1	...	.....	96				
70	0.61	0.28	1.02	0	0	2,900	54	1,100	21	500	+1,300
			1.28	1	...	.....	73				
71†	0.66	0.28	0.87	0	0	4,300	..	1,610	..	490	+2,810
			1.07	4	...	5,100					
212	1.16	0.56	1.10	0	0	3,000	..	1,270	..	400	+1,330
			1.64	1	...	2,620					
94	2.04	2.24	2.40	0	2	7,250	..	7,300	..	460	−560
			2.38	4	...	5,020					
205	1.43	1.95	.....	...	6	.....	..	4,200	59	440	
			2.35	1	...	3,520	49†	.....	..	...	−1,120
212	1.63	1.97	.....	...	1	.....	..	4,870	..	500	
			2.27	1	...	4,540	..	.....	..	...	−830

* Marked edema which disappeared after transfusion.
† Edema.

transfusion, which was about equal to the amount of blood transfused. The three cases in which there was a greater increase on addition of normal serum were a case of Banti's disease with ascites, a case of obesity and low blood volume, and a case in which posterior gastroenterostomy had been performed ten days before, the patient's blood count being 1,990,000, and the blood serum in all probability depleted.

In the series of patients with pernicious anemia, the blood counts indicated a greater exchange of fluid between tissue and blood. This, I believe, is more probably due to a greater abnormality of the serum, although the explanation is also plausible that there is a greater tendency for the native corpuscles to be destroyed. It is possible that in some cases, Case 71 for instance, both factors may have come into play. Of

TABLE 3.—*Change in Blood Count and Indicated Fluid Exchange Following First Transfusion of a Series, Compared with That Occurring Following Subsequent Transfusions*

Case	Count Before Transfusion	Difference	Diagnosis
Patients Receiving First Transfusion:			
1	4,600,000	—260,000	Secondary anemia
2	1,390,000	+280,000	Primary anemia
3	1,370,000	— 40,000	Primary anemia
4	1,190,000	+260,000	Primary anemia
5	2,870,000	—290,000	Malignancy
6	2,180,000	+370,000	Primary anemia
7	4,500,000	— 50,000	Jaundice
8	4,580,000	— 8,000	Malignancy
9	2,700,000	—220,000	Primary anemia
Av. for cases with positive change	1,590,000	+300,000	
Patients Receiving Second Transfusion:			
10	1,730,000	+460,000	Primary anemia
11	3,440,000	+300,000	Jaundice
12	2,420,000	+400,000	Secondary anemia
13	1,490,000	— 30,000	Primary anemia
14	1,160,000	+620,000	Primary anemia
15	1,290,060	+360,000	Primary anemia
16	1,640,000	+420,000	Primary anemia
17	3,070,000	—460,000	
18	1,580,000	+360,000	Primary anemia
Av. for cases with positive change	1,800,000	+430,000	
Patients Receiving Third to Fifth Transfusion:			
19	2,430,000	+210,000	Primary anemia
20	2,390,000	+300,000	Primary anemia
21	1,820,000	+520,000	Primary anemia
22	1,300,000	+330,000	Primary anemia
23	1,910,000	+570,000	Primary anemia
24	1,970,000	+530,000	Primary anemia
25	2,000,000	— 60,000	Primary anemia
26	1,700,000	+300,000	Primary anemia
27	2,270,000	+570,000	Primary anemia
28	3,030,000	+270,000	Secondary anemia
Av. for cases with positive change	2,090,000	+380,000	

Theoretical Increase in the Blood Count after Transfusion Calculated on the Basis of a 500 c.c. Transfusion at a Count of 4,440,000 Red Cells is Compared with the Actual Increase and Interpreted as Change in Volume

Transfusion	Actual Increase	Estimated Increase	Difference	Fluid Exchange, C.c.
Average Blood Volume of 3,800 C.c. Assumed:				
First	300,000	380,000	— 70,000	+
Second	430,000	330,000	+100,000	—160
Third to fifth	390,000	310,000	+ 80,000	—120
Average Blood Volume of 4,200 C.c. Assumed:				
First	300,000	340,000	— 40,000	+
Second	430,000	300,000	+130,000	—230
Third to fifth	390,000	280,000	+110,000	—180
Average Blood Volume of 500,000 C.c. Assumed:				
First	300,000	280,000	+ 20,000	— 60
Second	430,000	250,000	+180,000	—390
Third to fifth	390,000	230,000	+1,660,000	—330

a series of seven cases of first transfusions, there was no indication of a change in volume in one, and in another, practically none; in five there was an apparent increase in volume besides that added by transfusion, which ranged from 560 to 2,810 c.c. In three patients who had received previous transfusions, there was an apparent loss of fluid; in two of these, the determinations were not made until the day following the transfusion, and in the meantime it is possible that the bone marrow may have put out new cells, and so caused the unexplained increase, which gave the appearance of decreased blood volume.

Further data which are pertinent to the question were obtained from patients receiving transfusions of blood of the same group. In these cases blood volume estimates could not be made, but a comparison of the counts before and after transfusion offers evidence. For several days, counts were made on all patients referred for transfusion, and the data were classified according to the number of transfusions which had been previously given (Table 3). Of the nine first transfusions, six caused a reduction in the blood count; of these, three were given to patients with secondary anemia whose counts before transfusion were as high as, or higher than, the count of the blood transfused. The recipients, however, in three instances had low initial blood counts. In the three instances in which the transfusion raised the count, the average increase was 303,000 corpuscles for each cubic millimeter, on an initial average blood count of 1,590,000. Of nine second transfusions, only two caused a decrease in the initial count of the blood, and seven an increase, which averaged 430,000 corpuscles for each cubic millimeter, on an average initial count of 1,880,000. Of ten patients who were receiving from the third to fifth transfusion, only one had a lower count after the transfusion than before; the average increase in the eight other counts was 390,000, on an average initial count of 2,090,000. Without blood volume data, the significance of the counts which increased has been estimated on the basis of an assumed range of blood volumes, which would seem to cover the probabilities.

In the second paper of this series, the average blood volume of a series of patients with pernicious anemia, receiving blood transfusion for the first time, was 4,260 c.c. The average volume in a series reported by Keith,[4] some of whose patients had probably had several transfusions, was 4,360 c.c. As the average blood percentage by volume was lower, in proportion to the figure for the average blood volume, in my series than in Keith's, it seemed possible that in mine there may have been a larger proportion of tall subjects; therefore, to be on the safe side, I

4. Keith, N. M.: The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am. J. M. Sc. **165**:174-184 (Feb.) 1923.

have taken 3,800 as the first blood volume. This would be equivalent to 6.4 per cent. of the body weight of a subject weighing 130 pounds (59 kg.), too low an estimate for the average blood volume of the patients receiving their second to fifth transfusions. I have also assumed the blood volumes 4,200 and 5,000 c.c., which would be respectively 7.1 and 8.5 per cent. of the body weight of a subject weighing 130 pounds (59 kg.). The latter would seem the more probable estimate for the average blood volume of the patients who had received more than two transfusions. In the estimate of the probable count of the transfused blood, I used the average of a series of counts on citrated blood, taken in the same amount and prepared in the same operating room. This count was 4,440,000 corpuscles for each cubic millimeter. Transfusions of 500 c.c. were given in all cases.

In considering these cases in which there was an increase in the count resulting from transfusion, it was assumed that the initial average count of the patient's corpuscles was diluted by transfusion to $\frac{V - 500}{V}$ times the average initial count, V being the average blood volume after transfusion. It was assumed that the transfused blood was diluted after transfusion to $4{,}440{,}000 \times \frac{500}{V}$. The two figures added are the count after transfusion, provided no change in volume has taken place, and the difference between this and the initial count is the increase that should take place in the count on the basis of the assumed blood volume. The blood volume change was obtained by multiplying V by the factor, calculated blood count divided by actual blood count, and subtracting the product from V. There is obviously a slight error in these formulas, but it is of no importance in this connection. The calculations are appended to Table 3. With all three blood volume estimates, the calculations show that after the second to the fifth transfusions the corpuscle counts were greater than would be accounted for by the blood transfused, and indicated a passage of fluid from plasma to tissues. For the first transfusion, the two lower blood volume estimates give calculated increases which, in comparison with the actual increase, indicate a passage of fluid from tissue to blood, and even for the highest blood volume estimate, which is undoubtedly too high for a first transfusion, the estimated and actual counts are practically equal. This series shows a marked difference in tendency of direction of change in volume between the first transfusion of a series and the later ones. The transfusions were spaced about a week apart.

Since the blood from which all these data are derived was obtained by puncture of the ear, there was the possibility that, with the freer flow after transfusion, the lower count obtained might merely be due to the technic of taking the blood. This point was controlled in one

instance in which the Lewisohn blood volume method was compared with that of Ashby. The percentage of corpuscles in the blood taken from the vein of the patient before transfusion was 23.4 by the hematocrit reading; fifteen minutes after the transfusion, it was 23.1; the reading of the transfused blood was 43.6 per cent. Four hundred eighty cubic centimeters were given. The patient's blood volume after transfusion was estimated from the count of the unagglutinable corpuscles to be 4,450 c.c., or 8.2 per cent. of her body weight. The case was one of secondary anemia; there was no transfusion reaction. The blood from the basilic vein showed, in this instance, the same degree of decrease in corpuscle content after transfusion as the ear puncture revealed in the cases already cited.

SUMMARY AND CONCLUSION

Following the first transfusion, changes are likely to occur in the recipient's blood count so that destruction of the recipient's corpuscles or an addition of fluid from the tissues is observed within half an hour after the beginning of transfusion. As these changes are not associated with hematuria or any tendency toward reaction, and as they are apparently more apt to occur in patients whose condition is such that a reduced protein content might be expected, I consider it probable that they are due to change in volume caused by a higher osmotic pressure of the serum introduced. In patients who have been transfused recently, the chances that this apparent increase in blood volume will occur following a second transfusion are much diminished, and in the majority of cases there is indication that an exchange of fluid from blood to tissue occurs on transfusion. Among my studies of second and third transfusions, there was only one in which I had all the necessary data for determining this exchange, and in that study there was evidence of it. In the study of the change of count in a larger series of like group transfusions in which blood volume could not be determined, but in which a probable range of blood volume could be safely estimated, there was found, following most second to fifth transfusions, excess in the increase of the corpuscle count, which would indicate a passage of fluid from blood to tissue, while, following the first transfusions, the change in count indicated a passage of fluid from tissue to blood. Keith,[5] who uses the vital red method, has also reported observations of no increase in volume after transfusion.

In accounting for the difference between the osmotic pressure of the patient's and donor's bloods, one would expect to find, as one of the factors, a difference in protein content, either quantitative or qualitative,

5. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, 1919, Special Report No. 27.

such that a difference in the number of molecular aggregates might occur. Wells,[6] in his summary of the literature on the serum protein content in patients with pernicious anemia, says that the serum proteins are reduced, the decrease being in the serum globulin. Peters and Rubnitz,[7] on the other hand, report a higher protein content than normal in the serum of patients with severe anemia. So, apparently, both conditions are possible. That plasma volume may be abnormally high in patients with pernicious anemia has been reported by Keith. In line with the idea that the apparent tendency to exchange of fluid from tissue to blood, on repeated transfusion, is due to increase in osmotic pressure from increase in protein content would be my own data (fourth paper of this series), which seem to indicate that the blood volume of patients with pernicious anemia is usually greater following later transfusions than at the first transfusion of a series, even when there is no great change in the total cell volume. A series of transfusions apparently tends to stimulate an increase in plasma volume, probably owing to increase in protein content. It would seem probable that the protein content might be stimulated to an excess of increase, such that, after a series of transfusions, the difference between the osmotic pressure of the donor's and patient's plasma might be reversed.

If these discrepancies between the counts of the patient's blood before and after transfusion are in reality due to change in blood volume, they would be a source of error in any method for determining blood volume, which utilized the change of concentration of any constituent of the blood by transfusion; if, on the other hand, they are due to corpuscle destruction, they would still be a source of error to any method which utilized the change in concentration of the corpuscle content resulting from transfusion.

Although the data have been so collected that the changes are known to occur within half an hour after transfusion, it is very possible that they are of almost immediate occurrence. These changes bear no relationship to the occurrence of transfusion reactions.

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6. Wells, H. G.: Chemical Pathology, Ed. 3, Philadelphia, W. B. Saunders Company.

7. Peters, A. W., and Rubnitz, A. S.: Observations on the Chemical Pathology of the Blood in Pernicious Anemia and Other Severe Anemias, Arch. Int. Med. **26**:561-569 (Nov.) 1920.

ANATOMIC FINDINGS IN ESSENTIAL HYPERTENSION *

ARTHUR M. FISHBERG, M.D.
NEW YORK

The concept of essential hypertension includes those cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or from urinary obstruction. The clinical picture of essential hypertension is, as a rule, quite distinctive, and has become widely known, in recent years, through the publications of Huchard,[1] Janeway,[2] Allbutt,[3] Volhard [4] and others, in their respective countries. As a result of these studies, it is now possible to diagnose essential hypertension with a fair degree of certainty in the large majority of cases. But we are occasionally confronted at necropsy by a secondary (i. e., postnephritic) contracted kidney, despite the fact that the clinical features of the case gave no indication that the hypertension was associated with inflammatory disease of the kidneys. Because of such rather exceptional cases, essential hypertension cannot be unequivocally defined by the absence of clinical evidence of nephritis or of urinary obstruction, and it is necessary to add the word "anatomically" to the definition to prevent the inclusion of those cases of nephritis in which the identity is first revealed at the postmortem table. This definition is very seriously defective in that it defines the disease solely by exclusion, but, in our present ignorance of the causes of hypertension in general, it does not seem feasible to define essential hypertension in any more satisfactory way. Nevertheless, the consideration of essential hypertension as a distinct nosologic entity seems fully justified, both from a clinical and, as will be discussed below, from an anatomic point of view.

Essential hypertension, thus defined, is very much more common than chronic hypertension associated with inflammatory disease of the kidney. Of eighty-two cases of chronic hypertension coming to necropsy at the Montefiore Hospital, seventy-two, or 88 per cent., were instances of

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* From the Medical Division of the Montefiore Hospital.

1. Huchard: Traité clinique des maladies du coeur et de l'aorte, Paris, **1**:45-125, 1899.

2. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755-798 (Dec.) 1913.

3. Allbutt: Diseases of the Arteries, Including Angina Pectoris, London, **1**:378-454, 1915.

4. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914, pp. 210-246.

essential hypertension. However, it should be stated that the patients in the Montefiore Hospital are largely sufferers from chronic diseases, and that, therefore, the proportion of true nephritis is probably somewhat smaller than in the usual hospital service.

In the present paper, we desire to report on the anatomic findings in these seventy-two cases of essential hypertension and their interpretation.

ARTERIOLAR LESIONS

Cases of clinically typical essential hypertension in which neither renal nor arteriolar lesions of consequence were found at the necropsy have been described by various authors.[5] But it is evidently rather rare for such a case to come to necropsy, and one must agree with Hueck [6] that the existence of hypertension for more than a few weeks can usually be read in the arterial walls. Every one of our seventy-two cases of essential hypertension showed more or less marked but always clearly defined arteriolar changes. It is of great interest that the arteriolar lesions so constantly accompanying essential hypertension are essentially identical in the various organs, and of equal significance that, as will be seen below, they have a very characteristic distribution. To this well defined lesion of the arterioles, the term arteriolosclerosis has been aptly applied. As has long been known, arteriolosclerosis occurs most frequently and most markedly in the kidney, and it may, therefore, be best to describe first the evolution of the typical lesion in that organ.

The histologic picture of arteriolosclerosis develops somewhat differently in the smallest arterioles, the vasa afferentia, than in the next larger vessels, the vasa interlobulares. In the afferent arterioles, the first change noted is a deposition of so-called hyaline substance directly under the endothelium. Fortunate longitudinal sections show that the hyalinization does not occur uniformly along the course of the vas afferens, but usually begins close to the junction with the glomerular tuft. The highly refractile hyalin appears pink in ordinary hematoxylin-eosin preparations and yellowish-orange in sections stained by van Gieson's method. In the earliest stages, this hyalin is not stained by sudan III, but later on it quite frequently undergoes fatty change and gives lipoid reactions. Hueck [6] believes that the hyaline substance is semifluid and, in the early stages at least, causes little increase of resistance to the flow of blood. In the larger interlobular arterioles, the first change observed is apparently hyperplasia of the internal elastic membrane with reduplication and the formation of multiple lamellae

5. Pal: Ueber Herzhypertrophie und Hypertonie, Med. Klin. **15**:662, 1919. Von Monakow: Blutdrucksteigerung und Niere, Deutsch. Arch. f. klin. Med. **133**:129, 1920.

6. Hueck: Anatomisches zur Frage nach Wesen und Ursache der Arteriosclerose, München med. Wchnschr. **67**:835, 1920.

(Jores' hyperplastic type of intimal thickening). The hyperplastic elastic tissue undergoes regressive changes with the appearance of lipoid and hyaline substance and reactive proliferation of the neighboring connective tissue, gradually resulting in marked narrowing of the lumen which may slowly go on to complete obliteration. In the earliest stages of the process in both afferent and interlobular arterioles, the media do not present any marked changes, but a progressive atrophy of the muscle cells with fatty and hyaline change then sets in and, finally, fibrous replacement. As far back as 1868, Johnson [7] described hypertrophy of the media as a characteristic in granular kidney and most current textbooks contain the same statement, but, as a matter of fact, one finds in arteriolosclerosis a gradual and progressive degenerative atrophy of the medial muscle with replacement fibrosis. This is in a certain contrast to the larger vessels in essential hypertension, as well as to the arterioles in true nephritis, in which I have occasionally observed an apparent medial hypertrophy. The latter is, however, difficult to ascertain with certainty, as Jores [8] pointed out, because of deceptive appearances caused by postmortem contraction. The progressive intimal thickening just described naturally leads to a progressive narrowing of the lumen. But to this there is a noteworthy exception, first described by Loehlein,[9] which I have repeatedly been able to confirm. In the early stages of the hyaline change in the vasa afferentia, these vessels are often tremendously dilated at their entrance into the glomerular tuft, warranting Loehlein's description of the dilatation as "lakelike." The dilatation also may involve the first divisions of the vas afferens, so that in longitudinal sections a Y-like figure is seen, often packed with red cells. Only the terminal part of the vas afferens is thus dilated, and it may follow on a marked constriction.

It is, of course, of primary importance whether these arteriolar lesions, found in practically all cases of essential hypertension, also occur in patients with normal blood pressure. In vasa interlobulares, reduplication of the internal elastic lamina is often seen beginning with the fourth decade, or even earlier, and usually attains a considerable extent in elderly people, though not approaching that seen in cases of chronic hypertension of the same age. Hyalinization of the vasa afferentia to a slight degree is often seen at a later period of life, but I have not seen marked hyalinization of the afferent arterioles in a case with normal tension (except in the vicinity of inflammatory lesions, e. g., pyonephrotic

7. Johnson: On Certain Points in the Anatomy and Pathology of Bright's Disease, Tr. Med.-Chir. Soc. **51**:57, 1868.

8. Jores: Ueber die Arteriosclerose der kleinen Organarterien, Virchows Arch. f. path. Anat. **178**:374, 1904.

9. Loehlein: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917.

lesions). In the spleen, on the contrary, well marked and progressive hyalinization is physiologic and sets in quite early in life. Principally, the central arterioles of the malpighian bodies are involved. Thus, Herxheimer [10] found, in an investigation of 1,100 spleens, that hyalinization was present in 15 per cent. of those under 10 years of age, in more than half of those between 30 and 40, and in three-quarters of the patients over 60. The hyaline substance found in the splenic arterioles of people with normal blood pressure is apparently identical with that in cases of hypertension; it also often undergoes fatty change. The physiologic occurrence of hyaline change in the splenic arterioles often renders it difficult to decide whether or not changes observed in these vessels in a case of hypertension have any correlation with the high blood pressure.

DISTRIBUTION OF THE ARTERIOLAR LESIONS

It has been known since Gull and Sutton's [11] pioneer communication that arteriolosclerosis is not always confined to the arterioles of the kidney; in fact, it is quite common usage to speak of "generalized arteriosclerosis" of the smaller radicals, implying the existence of a system disease of the arterioles of the body. Most investigators have confined their examination of the smaller vessels in essential hypertension to those of the kidney. But the arterioles in other organs have also received some attention. Thus, Jores [8] found that the lesions of the small arterioles which he described as the pathogenetic agent in the primary contracted kidney also were to be found in the arterioles of other organs. Münzer,[12] in a number of publications, has championed Gull and Sutton's half century old view that nonnephritic hypertension is secondary to a generalized arteriocapillary fibrosis; to explain the frequent absence of any visible changes in the arterioles throughout the body, he invokes the inadequacy of our present histologic methods. This view has been disputed by Fahr,[13] who maintains the predominant rôle of the lesions of the renal arterioles, and points out that the small vessels of the skin, voluntary muscles and intestines are very rarely involved. Hasenfeld [14] and others have claimed that essential hypertension is due to sclerosis of the arterioles of the splanchnic area. In

10. Herxheimer: Ueber das Verhalten der kleinen Gefaesse der Milz, Berl. klin. Wchnschr. **54**:82, 1917.

11. Gull and Sutton: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease, Tr. Med.-Chir. Soc. **55**:273, 1872.

12. Münzer, E.: Gefaessklerosen, Wien.-Arch. f. inn. Med. **2**:1 (Dec.) 1920.

13. Fahr: Ueber die Beziehungen von Arteriolensklerose, Hypertonie, und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922.

14. Hasenfeld and Hirsch: Ueber die Herzhypertrophie bei Arteriosklerose, Deutsch. Arch. f. klin. Med. **59**:193, 1897.

an extensive investigation, Evans [15] found that the small vessels of the spleen are involved about as often as those of the kidney, while the minute branches of the coronary arteries are never affected.

In view of these differences of opinion as to the distribution of the arteriolar lesions associated with hypertension, we have systematically examined the arterioles of the various organs in the seventy-two cases of essential hypertension on which this study is based. The findings are summarized in the following table. It is to be emphasized that this table has reference only to the lesions found in the minute arterioles, i. e., those corresponding in size to the vasa interlobulares and vasa afferentia of the kidney. For lack of any more adequate method, we have expressed the grade of the arteriolar lesions by the symbols N for normal, 1 plus, 2 plus, 3 plus and 4 plus. A dash means that the organ was not investigated. The word normal has, of course, been used in a relative sense, taking into consideration those changes which physiologically occur in the arterioles of the various organs with advancing years, and which are, therefore, not correlated with the hypertension. The hyalinization that occurs normally in the arterioles of the spleen (discussed in the foregoing) renders particularly difficult the investigation of the smaller radicals of that organ, and the findings in the splenic arterioles tabulated below must therefore be taken with some reserve.

The cutaneous arterioles were examined in seventeen cases and those of the voluntary muscles in fifteen; in no instance was arteriolosclerosis noted.

If Table 1 is studied, it is seen that the organs fall into three groups with regard to the involvement of their arterioles in essential hypertension:

1. *Kidney.*—In essential hypertension, the arterioles of this organ are involved much more frequently and far more intensely than those of any other portion of the body. In every one of the seventy-two cases examined, the renal arterioles were affected. Moreover, in almost every instance, the severity of the arteriolar lesions in the kidney greatly exceeded that in any other organ. In ten of the cases, the arterioles of the kidney were the only ones affected. However, in several cases, the involvement of the renal arterioles was only slight; these will be discussed in connection with the interpretation of the lesion.

2. *Spleen, Pancreas, Liver and Brain.*—In cases of essential hypertension, arteriolosclerosis is a common finding in these organs. Involvement of the splenic arterioles occurs in about two thirds of the cases, the pancreatic in about half, the hepatic in less than a third, and the

15. Evans: A Contribution to the Study of Arteriosclerosis, Quart. J. Med. **14**:215, 1920.

TABLE 1.—*Distribution and Intensity of Arteriolar Lesions in Essential Hypertension*

Necropsy No.	Age	Blood Pressure: Systolic	Blood Pressure: Diastolic	Kidney	Heart	Lung	Spleen	Liver	Pancreas	Brain	Gastro-Intestinal Tract	Suprarenals
1	46	240	150	+++	N	N	N	N	+	—	—	N
2	54	228	100	+++	N	N	+	N	+	+	N	+
3	70	170	100	+++	N	N	N	N	N	N	N	N
4	70	210	94	+++	N	+*	+	N	++	—	—	+
5	75	205	...	+	N	N	+	N	N	—	—	N
6	63	180	110	+++	+	N	+	N	+	—	—	+
7	59	210	118	+++	N	N	N	N	N	—	N	N
8	50	High		+++	N	N	N	+	N	N	N	N
9	53	160	100	+	N	N	+	N	N	N	—	—
10	54	195	130	+++	N	N	+	+	+	+	N	+
11	59	190	130	+++	N	N	++	+	+	N	—	N
12	83	210	160	+++	N	N	N	N	+	—	—	+
13	59	140	100	+++	N	N	N	N	N	—	N	N
14	58	210	100	++	N	N	N	+	N	N	N	N
15	56	210	98	++++	N	N	++	N	+	—	+	+
16	70	170	102	+++	N	N	+	N	+	++	N	N
17	64	196	110	++	N	N	N	N	N	N	N	N
18	56	214	114	+++	N	+*	+	N	N	—	—	—
19	75	170	96	++	N	N	+	N	N	+	—	N
20	80	255	165	++++	N	N	++	+	+	—	+	+
21	70	264	145	+++	—	N	+	+	+	N	—	N
22	55	240	110	+++	N	N	+	+	N	N	—	N
23	60	180	100	+++	N	N	N	N	—	N	—	N
24	55	200	114	++	N	N	N	N	—	N	—	N
25	62	170	94	+++	N	N	N	N	N	—	—	N
26	56	265	130	+++	N	N	+	N	N	N	—	+
27	60	160	88	++	N	N	N	+	+	—	—	N
28	62	180	100	++	N	N	+	N	+	—	N	N
29	72	170	100	+++	N	N	N	N	+	—	N	—
30	54	225	100	++++	N	N	+	N	++	—	N	+
31	56	270	130	++++	N	N	+	+	—	N	—	—
32	40	175	120	+++	N	N	N	N	N	—	N	N
33	..	150	100	+	N	N	—	N	N	—	N	N
34	60	200	...	+++	N	N	—	N	+	N	—	—
35	87	204	108	+++	N	N	—	++	+	—	+	+
36	52	238	140	+++	N	N	+	—	N	—	N	—
37	75	194	120	+	N	N	N	N	+	N	—	N
38	60	240	135	+	N	N*	+	N	N	—	N	—
39	58	140	95	++	N	N	N	N	N	N	—	N
40	65	195	105	++++	..	N*	++	+	++	—	N	—
41	83	220	110	+++	..	N*	+	+	+	—	N	N
42	54	180	135	+	N	N	N	N	+	—	—	N
43	70	232	130	++	N	N	+	N	N	N	—	N
44	52	180	110	++	N	N	++	N	N	+	N	+
45	71	190	...	+++	N	N	+	N	N	—	N	—
46	65	190	92	+++	N	N	+	N	—	—	—	—
47	69	210	110	+++	N	N	—	N	N	N	—	N
48	73	High		++	N	N	N	N	+	N	—	—
49	72	170	90	++++	N	N	+	+	N	—	—	+
50	63	210	130	++++	N	N	+	+	+	—	N	N
51	60	140	110	+	N	N	N	N	N	N	—	N
52	69	180	95	+	N	N	+	N	N	—	N	N
53	58	202	128	+	N	N	N	+	N	+	N	N
54	69	150	110	+	—	—	+	—	N	—	—	—
55	96	140	90	+++	N	N	+	N	+	—	—	+
56	53	190	90	++	N	N	N	+	N	—	N	N
57	60	204	130	+++	N	N	+	N	+	—	—	N
58	52	275	165	+	N	N	+	N	+	—	—	N
59	56	230	125	+++	N	N	++	+	+	N	N	N
60	63	200	125	+++	N	N	+	+	N	—	N	—
61	62	165	120	+++	N	N	+	N	+	—	—	+
62	60	High		++++	N	N	+	N	+	—	—	N
63	72	162	100	+++	N	N	+	N	—	N	—	N
64	75	160	80	++++	N	+*	+	N	N	—	N	N
65	78	188	96	++	+	—	+	+	N	—	N	N
66	72	High		+++	N	N	+	N	N	—	N	N
67	46	180	...	++	N	N	N	N	N	N	—	—
68	62	150	90	+	N	N	+	N	+	N	—	N
69	47	260	130	+++	N	N	+	N	+	N	N	+
70	34	225	145	++	N	N	+	+	+	N	—	+
71	71	190	92	+++	N	N	+	+	+	—	N	N
72	57	175	100	++	N	N	N	+	N	—	—	N
Total cases examined				72	68	70	68	70	68	31	34	59
Arteriolar lesions present.				72	2	0*	45	21	23	6	3	17

* These patients had mitral stenosis and the lesions of the pulmonary arterioles are to be attributed to the valvular lesion and not to the hypertension; they are, therefore, not considered in the totals.

cerebral in about one fifth of the cases. But the lesion usually is not very marked, rarely being even nearly as intense or diffuse as in the kidney. There is no constancy about the involvement of these organs; any one or more of them may be involved in a given case. The most marked arteriolar changes in these organs are found only in association with a very advanced process in the renal arterioles. Another organ in which arteriolosclerosis is quite often found is the suprarenal gland, which was involved in seventeen of sixty cases. Here, the arteriolar thickening is best seen in the connective tissue capsule. But considerable hyaline change of the arterioles of this organ is not uncommon in persons with normal arterial tension.

3. *Skin, Skeletal Muscles, Myocardium, Lung, Gastro-Intestinal Tract and Thyroid.*—In these organs, the lesions of arteriolosclerosis are found only rarely and then to only an insignificant extent. Thickening of the smaller arterioles of the lung is occasionally seen when the hypertension is accompanied by mitral stenosis, an association which is not uncommon, but is then attributable to the valvular lesion and consequent increase of pressure in the lesser circuit. I have not seen any clearly defined example of the lesion in the voluntary muscles, or more than minimal involvement of the arterioles within the myocardium, and that only twice in sixty-eight cases. In two instances, slight intimal thickening of arterioles in the pericardial tissues was seen without any corresponding change in the vessels of the heart muscle proper. The stomach and intestines are only very uncommonly involved by arteriolosclerosis, and then the lesion is very slight. I have not found any basis for the view that essential hypertension is due to sclerosis of the splanchnic vessels. These findings are in essential agreement with those of previous authors who have examined various organs. Thus, Evans [15] has noted the rarity of lesions of the smaller arterioles (which he terms diffuse hyperplastic sclerosis instead of the term arteriolosclerosis used here) in the heart muscle and gastro-intestinal tract; Fahr,[13] their rarity in the skin, voluntary muscles and gastro-intestinal tract, and Watanabe [16] found thickening of the small arterioles of the skin in only six of 116 cases.

In the testis, prostate and pituitary gland, which were examined in a small number of instances, arteriolosclerosis was not noted. The ovary and uterus were not studied because regressive changes of somewhat different histologic appearance are frequent findings in association with menstruation, pregnancy and senile involution. I had no opportunity for anatomic study of the minute arterioles of the retina; this would have

16. Watanabe, S.: Ueber die Arteriosklerose der Hautgefaesse, Schweiz. med. Wchnschr. **51**:780 (Aug. 25) 1921.

been desirable as it has recently been shown by O'Hare and Walker [17] that the retinal arterioles of a size to be seen ophthalmoscopically are usually thickened in essential hypertension.

It is of interest to compare the incidence of arteriosclerosis in the various organs with the frequency of senile arteriosclerosis of the large vessels in these organs.

The figures for arteriosclerosis in Table 2 are taken from Brooks' [18] investigation of 400 cases. He gives no figures for the vessels of the extremities, but the great frequency of senile arteriosclerotic changes (including here medial calcification) in the radials, tibials and other large arteries of the extremities is a matter of everyday observation. On the other hand, it was seen above that arteriolosclerosis is exceedingly rare in the tissues making up the extremities, i. e., muscle and skin.

This comparison of the incidence of lesions of the large and small vessels in the various organs of the body thus reveals no parallelism in their distribution. On the contrary, a sharp divergence is to be noted, arteriolosclerosis invariably affecting the kidney, with the spleen,

TABLE 2.—*Incidence of Arteriosclerosis and Arteriolosclerosis in Various Organs*

	Arteriosclerosis, per Cent.	Arteriolosclerosis, per Cent.
Extremities	High	0
Heart	73	3
Brain	36	19
Kidney	23	100
Pancreas	20	49
Liver	12	30
Spleen	10	06
Lung	5	0

pancreas and liver next in order of frequency, while large vessel atherosclerosis has its sites of predilection in the extremities, heart and brain. Neither lesion occurs in the arteries of the lesser circulation in correlation with essential hypertension.

The study of the distribution of the arterial lesions thus affords a point of view from which it seems very probable that different factors enter into the pathogenesis of arteriolosclerosis than are concerned in the production of atherosclerosis of the large vessels. This is confirmed by certain other evidence:

1. Arteriolosclerosis of any considerable degree is constantly accompanied by essential hypertension, while senile arteriosclerosis apparently has little correlation with hypertension.

2. The age incidence of arteriolosclerosis is somewhat different from that of large vessel sclerosis. The maximum age incidence of arteriolo-

17. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924.

18. Brooks: A Preliminary Study of Visceral Arteriosclerosis, Am. J. M. Sc. **131**:778, 1906.

sclerosis is that of essential hypertension, i. e., middle life, while large vessel lesions continue to increase in frequency with advancing age, being most common in very old persons.

3. It has been shown by the Aschoff school that the large vessel lesions can be produced—in herbivora, at least—by derangements of lipoid metabolism. In uncomplicated experiments of this nature, the small vessels are not affected.

SIGNIFICANCE OF THE ARTERIOLAR LESIONS

The interpretation of the arteriolar lesions resolves itself into the old question of the relation they bear to the hypertension of which they are a constant accompaniment. Half a century ago, two theories were formulated, each of which still has its advocates:

1. Gull and Sutton's [11] view [19] that the disease of the arterioles is primary and causes the hypertension by mechanically narrowing the peripheral stream bed, thus increasing the peripheral resistance.

2. Johnson's [7] theory of substances failing of excretion by a primarily diseased kidney causing a spasm of the peripheral arterioles and thus functionally increasing the peripheral resistance. According to this view, the hypertension would be the cause of the arteriolar lesions.

That the hypertension is due to the mechanical increase in resistance caused by organic lesions of the smaller arterioles does not seem possible, in view of the limited arteriolar areas that are thus affected even in the most extensive cases. We have seen that the arteriolar lesions are usually severe only in the kidneys, and that while a few other organs (spleen, liver, pancreas and brain) may be involved to a slight or, at most, to a moderate extent, the great mass of the arterioles of the body, in the striped muscles, skin, gastro-intestinal tract and heart, show practically no lesions. It is well known from physiologic experiments that any increased peripheral resistance in an organ is immediately compensated for by a vasodilatation elsewhere in the body, so that no increase in the general blood pressure occurs. The arteriolosclerosis would have to involve very extensive regions were it to increase mechanically the peripheral resistance by an amount too great to be compensated for elsewhere; i. e., it would have to be a true generalized arteriolosclerosis. But it was shown above that it involves only a small

19. Peculiarly enough, Gull and Sutton did not actually observe the intimal thickening which we now know to be the most striking change in the small vessels. They thought the thickening of the arterioles was due to a "hyalin-fibroid" change in the adventitia. This is shown by their illustrations and their statement (p. 283) that "the morbid changes we have observed occur chiefly outside the muscular layer." The error of these brilliant and original observers is readily understood when it is recalled that their histologic methods consisted in the study of frozen sections in which the nuclei were stained by carmin.

fraction of the great arterial periphery; the vast majority of the arterioles are left with an unnarrowed lumen. In brief, a true generalized arteriolosclerosis does not exist in association with essential hypertension and, therefore, cannot be the cause of the latter.

It was pointed out above that lesions of the arterioles identical in nature with the arteriolosclerosis associated with chronic hypertension are a physiologic accompaniment of advancing years. Hyalinization of the smallest arterioles of the spleen begins to appear quite early in life; in middle-aged people, elastic hyperplasia is found in slightly larger arterioles in various organs, while late in life a slight degree of hyalinization of the vasa afferentia of the kidney can often be observed. These changes are a manifestation of the wear and tear to which the arterioles, the effectors of the never resting vasomotor nerves, are subject with advancing years. The arteriolosclerosis of essential hypertension may rationally be regarded as merely a pathologic exaggeration of these physiologic changes manifesting the tremendously increased strain put on the arterioles by the heightened blood pressure. The exact mechanism by which the increased strain of hypertension causes the arteriolar lesions is evidently complex and as yet totally unexplained; it does not consist solely in the increased blood pressure from within, for in that event the arteriolar lesions would be diffuse and not confined to a few organs, as we have found to be the case. Another of our findings which we have been unable to explain is the markedly atrophic condition of the medial musculature of the diseased arterioles. On the basis of the theory that essential hypertension is caused by increased tonus of the peripheral arterioles—and this is a theory supported by much cogent evidence—one would expect, by analogy with other tubular organs, that the medial musculature would be hypertrophic, as is the elastic tissue. But we have pointed out above that a progressive atrophy is the rule in essential hypertension.

RENAL LESIONS

Though instances of simple chronic hypertension which have not evolved from antecedent inflammatory disease of the kidney are here considered as cases of essential hypertension, nevertheless, renal lesions form an almost constant finding when such cases come to necropsy. The relation of these renal lesions to the high blood pressure has occupied the focal point of all discussions relative to the pathogenesis of the hypertension. It was formerly believed that the renal lesions are the results of a chronic interstitial inflammation, whence the name for these cases of chronic interstitial nephritis, still in common use. But the investigations of Ziegler,[20] Jores [8] and numerous others have demon-

20. Ziegler: Ueber die Ursachen der Nierenschrumpfung, Deutsch. Arch. f. klin. Med. **25**:586, 1880.

strated beyond cavil that the pathogenetic factor in these cases is the arteriolosclerosis, and that the lesions of the renal parenchyma are secondary to the disease of the minute arterioles. Nevertheless, the Romberg [21] school and a considerable, though diminishing, number of others still hold that the cause of all persistent hypertension is the renal lesion. The untenability of this view is, I believe, shown by study of the histologic changes in essential hypertension.

As mentioned above, cases have been described by various authors in which chronic arterial hypertension is unaccompanied by any renal lesion. In our series of seventy-two cases, we were not fortunate enough to observe such an instance, but there were several in which maximal hypertension was associated with only minimal renal lesions.

REPORT OF CASES

Case 1.—M. L., a man, aged 52, had a history of progressive cardiac insufficiency, but nothing in it pointing to preceding acute nephritis. The blood pressure was 275 systolic, and 165 diastolic. No evidence of renal insufficiency was seen.

Necropsy was performed. The cause of death was diagnosed as coronary thrombosis. The heart weighed 810 gm.; there was great hypertrophy and dilatation, most marked in the left ventricle. The kidneys weighed 370 gm., and were slightly enlarged. The capsule stripped readily, revealing a smooth surface except for a few scattered depressions. Microscopically, an infarct was seen. Some of the vasa interlobulares showed moderate hyperplastic intimal thickening, but most were unaffected. A few of the vasa afferentia showed slight hyalinization. Here and there, a hyaline glomerulus and atrophic tubule were seen, but the parenchyma in general was excellent, the only diffuse change seen being moderate cloudy swelling of the tubular epithelium, obviously recent.

Case 2.—J. S., a woman, aged 58, had a cerebral hemorrhage three months before admission. The systolic blood pressure was 202, the diastolic 128. There was myocardial insufficiency.

Necropsy was performed. The causes of death were diagnosed as bronchopneumonia and pulmonary edema. The heart weighed 400 gm.; there was left ventricular hypertrophy and dilatation. The kidneys weighed 310 gm.; their surface was smooth. Except for some elastic hyperplasia in the larger arterioles and a few slightly hyaline vasa afferentia, the intimate vasculature of the kidney appeared normal. There were only very few hyaline glomeruli with atrophic tubules; the parenchyma in general revealed no long standing change.

From these cases, it is seen that very marked chronic hypertension may exist in the presence of renal changes consisting solely in slight arteriolosclerosis with consequent obliteration of a very small number of glomeruli and their appertaining tubules. The injury to the renal parenchyma may be so slight that it is necessary to search the sections carefully to discover it. It is known from ablation experiments that about three quarters of the renal parenchyma may be removed without any renal insufficiency manifesting itself. Moreover, the beautiful

21. Romberg: Krankheiten des Herzens und der Gefaesse, Stuttgart, 1921, p. 582.

experiments of Richards [22] have shown that only a fraction of the glomeruli (and presumably also of their tubules) work at the same time. In view of this enormous factor of safety possessed by the kidney, it seems impossible that the destruction of such a vanishingly small proportion of the renal parenchyma as is often found at the necropsy of cases of essential hypertension could, by depressing any of the functions of the kidney, entail such systemic consequences as hypertension.

Another anatomic consideration points in the same direction: The kidney is made up of a large number of functionally equivalent units, each consisting of a glomerulus and a long uriniferous tubule. Each such unit (nephron) is, so to speak, a miniature kidney in itself. Moreover, the vas afferens is a miniature renal artery, for, after emerging from the glomerulus as the vas efferens, it forms the sole or principal blood supply of the corresponding proximal and distal convoluted tubules. In essential hypertension, the injury to the kidney consists in the successive destruction of one such unit (miniature kidney) after another, for when the glomerulus becomes hyalinized as a result of the arteriolosclerotic process in its vas afferens, the corresponding tubule also atrophies. Obliteration of the glomerulus entails atrophy of the corresponding tubule for two reasons:

1. The sole or principal blood supply of the convoluted tubules is furnished by the vas efferens of the corresponding glomerulus.

2. Disuse atrophies the tubular epithelium, which no longer has the glomerular filtrate to work on.

In view of this successive destruction of complete renal units, there can be no question of injury to one of the partial functions of the kidney while the others remain intact. (This could only occur if there were a great difference in the factors of safety for the different partial functions, a view for which I know of no adequate evidence.) There must be, rather, a quantitatively equal reduction in all the functions. In the vast majority of cases of essential hypertension, however, such of the functions of the kidney as we are able to measure are for a long time not appreciably depressed. It does not, therefore, seem justified to hold that any one substance (e. g., one with pressor properties) is retained while those which we can measure are excreted normally.

FINDINGS WHEN ESSENTIAL HYPERTENSION IS COMPLICATED BY RENAL INSUFFICIENCY

Contrary to views widely held prior to the development of adequate methods for studying kidney function, it is now generally appreciated that the large majority of patients suffering from essential hypertension do not develop any significant renal insufficiency. It has been seen, in the foregoing section, that the anatomic findings would not lead us

22. Richards: Kidney Function, Harvey Lectures **16**:163, 1920-1921.

to expect inadequate renal function, for the lesions in the kidney are focal and not diffuse. The usual causes of death are directly attributable to the increased mechanical strain under which the circulatory apparatus labors (cardiac insufficiency and cerebral vascular insults) or intercurrent diseases. However, in a certain, though small, proportion of cases, the kidney function becomes inadequate. In our seventy-two cases with necropsies, five, or 7 per cent., of the patients died with renal insufficiency. This is a much smaller incidence of uremia than is found in chronic nephritis.

What is the cause of renal insufficiency in this small proportion of cases of essential hypertension, while the vast majority (93 per cent. of our series) complete the course of their disease with intact kidney function? This question of the pathogenesis of renal insufficiency in essential hypertension was first systematically attacked on the basis of comparison of the results of modern renal function tests with the postmortem findings by Volhard and Fahr [23] in their well known monograph of 1914. They divided the cases of essential hypertension into two groups:

1. Pure (benign) hypertension without renal insufficiency. In these cases (making up the vast majority of the total), the kidneys exhibit only foci of arteriolosclerotic scarring, while between these scarred areas there is left ample parenchyma to carry on the excretory functions.

2. The combination form (Kombinationsform) or malignant hypertension, in which renal insufficiency is superimposed on a previously existent pure hypertension. In such uremic cases, they found, in addition to the arteriolosclerotic foci, glomerular and other changes which they did not believe could be explained solely as secondary to the mechanical effects of the small vessel sclerosis. The glomerular findings were akin to those noted in cases of acute and subacute nephritis, consisting of proliferation of the epithelium of Bowman's capsule and of the endothelial cells of the glomerular capillaries, slight accumulation of leukocytes in the capillary loops and exudation into the capsular space. These changes they considered as inflammatory in nature and as evidencing the addition of a toxic nephritis to the preexistent arteriolosclerosis. This nephritic addition was held responsible for the onset of renal insufficiency.

While the clinical utility of Volhard and Fahr's division of cases of essential hypertension into two classes depending on the presence or absence of renal insufficiency has been generally recognized, their conception that the onset of uremia is attributable to a superadded nephritis has met with spirited opposition on the part of most pathologic anatomists

23. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914, p. 80.

(Loehlein,[9] Jores [24] and Herxheimer [25]). The latter admit the existence, in a relatively slight degree, of the findings described by Volhard and Fahr, but believe them due solely to the vascular lesions, and do not consider them evidence of the addition of a toxic inflammatory component. In more recent publications, Volhard and Fahr, while maintaining the accuracy of their original observations, have modified their conception of the pathogenesis of the renal insufficiency. Volhard [26] now believes the onset of inadequate renal function in a case of essential hypertension to be coincident with the occurrence of a general vasoconstriction, which has among its consequences ischemia of the glomeruli, albuminuric retinitis and the general pallor of the skin which is almost always found in renal insufficiency (even in the absence of anemia) in place of the previous plethoric appearance. Fahr,[27] on the contrary, holds that the lesions of the kidney in cases with renal insufficiency are due to an affection of the arterioles different from the arteriolosclerosis found in benign hypertension. This affection he describes as a rapidly progressive necrotizing arteritis of the renal arterioles, which soon impedes the renal circulation sufficiently to cause uremia. He terms the disease malignant sclerosis, in contradistinction to the benign sclerosis of uncomplicated hypertension. I have not been able to find the inflammatory arteriolar changes described by Fahr in essential hypertension with uremia, though such inflammatory changes of the arterioles are occasionally seen in nephritis.

Of the seventy-two cases of essential hypertension given in Table 1, in only five was renal insufficiency present, manifested by nitrogen retention and symptoms of uremia. In four others, there was moderate increase of nonprotein nitrogen in the blood without other clinical evidence of renal insufficiency or symptoms of uremia. Study of the anatomic changes in the seventy-two cases tabulated indicates that instances of essential hypertension with accumulation of nitrogen in the blood are of three varieties, anatomically characterized by:

1. Coalescence of the arteriolosclerotic foci.
2. Occurrence of more or less diffuse reactive glomerular changes.
3. Evidence of cardiac insufficiency.

1. *Coalescence of the Arteriolosclerotic Foci.—A priori,* it would seem that the usual cause of kidney insufficiency in essential hypertension with its accompanying arteriolosclerosis would be the successive obliteration of one area of parenchyma after another till the margin of safety

24. Jores: Ueber den pathologischen Umbau von Organen, Virchows Arch. f. path. Anat. **221**:14, 1916.
25. Herxheimer: Ueber die genuine arteriolosklerotische Schrumpfniere, Beitr. z. path. Anat. u. z. allg. Path. **64**:297, 1918.
26. Volhard: Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.
27. Fahr: Ueber Nephrosclerose, Virchows Arch. f. path. Anat. **226**:119, 1919.

has been exceeded. But while this is the usual mechanism in chronic nephritis, in essential hypertension it evidently occurs in only a very small proportion of the cases. In the extensive material reported in their monograph, Volhard and Fahr [28] did not see one instance of this type, but mention having been shown such material by Aschoff. In our series, there was one uncomplicated case of this variety, and another case in which both tremendous obliteration of parenchyma and cardiac failure played parts.

Case 3.—D. L., a woman, aged 54, had blood pressure 225 systolic, 100 diastolic. Blood chemistry findings were: urea nitrogen, 128; uric acid, 8.5; creatinin, 4.1, and sugar, 130 mg. per hundred cubic centimeters. Phenolsulphonephthalein excretion after intramuscular injection was less than 5 per cent. in two hours. Dilution and concentration tests showed the specific gravity to be fixed at 1.008-1.009. Albuminuric retinitis was present. Necropsy revealed the heart to weigh 680 gm. The finely granular kidneys together weighed only 160 gm. There was extreme arteriolosclerosis of the vasa interlobulares and vasa afferentia, which, in many instances, had progressed to complete obliteration of the lumen. Almost all the parenchyma had been obliterated and replaced by cellular connective tissue. Nearly all the glomeruli had been completely hyalinized. There were islands of dilated tubules lined by low epithelium. A few regenerated tubules were seen. The few glomeruli that were not obliterated were hypertrophic and exhibited no proliferative or exudative changes. There was little round cell infiltration.

In the foregoing case, the gradual obliteration of the glomeruli and their appertaining tubules finally progressed so far that compensation by the vicariously functioning remaining units became impossible. In the following case, destruction of the renal parenchyma had not proceeded quite so far, but cardiac failure precipitated the renal insufficiency while there was still a rather small amount of intact kidney tissue.

Case 4.—M. R., a woman, aged 56, had blood pressure 270 systolic, 130 diastolic. The urea nitrogen, on admission, was 19.6, then rose to 48.6 mg. per hundred cubic centimeters. Phenolsulphonephthalein excretion was first 9.5 per cent., then diminishing to 2.5, and finally to 0 per cent. in two hours. The specific gravity of the urine varied (spontaneously) between 1.013 and 1.016. Albuminuric retinitis was present.

Necropsy was performed. The heart weighed 430 gm. There was marked atherosclerosis of the larger coronary branches, one of which was freshly thrombosed (probably immediate cause of death). There was extensive myomalacia cordis. The red, granular kidneys together weighed 200 gm. There was extreme arteriolosclerosis. There were very many hyaline glomeruli and great fibrous replacement of the parenchyma. But there were a considerable number of apparently intact glomeruli which were congested. From the amount of uninjured parenchyma, one would not expect severe renal insufficiency. The onset of the latter was evidently precipitated by cardiac failure, due to the very severe coronary artery disease.

2. *Occurrence of Reactive Glomerular Changes.*—These are the cases described by Volhard and Fahr (discussed above) as the combination form. The arteriosclerotic process is well marked, but between the

28. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914, p. 65.

areas of hyalinized glomeruli and atrophic tubules there are considerable portions which have not undergone arteriolosclerotic atrophy. These glomeruli present, to a varying degree, proliferative and exudative changes. Three such cases were included in the foregoing series.

CASE 5.—E. I., a man, aged 47, known to have had hypertension for two years before admission, complained of headache, weakness and increasing irritability for the last six months. He was irrational when admitted. There was no cyanosis, dyspnea or edema. The blood pressure ranged from 230 systolic, 120 diastolic, to 240 systolic, 170 diastolic. The urea nitrogen was 68.9, later, 89.7; uric acid, 4, and creatinin 4.1 mg. per hundred cubic centimeters. The phenolsulphonephthalein output after intramuscular injection was 7 per cent. in two hours. Examination of the urine revealed: specific gravity, 1.010, a heavy trace of albumin and a few hyaline casts. The concentration test could not be done. Ophthalmoscopic examination was neglected. Soon after admission, the patient went into coma and died, eight days after entrance.

Necropsy was performed. The heart weighed 760 gm.; there was marked left ventricular hypertrophy and dilatation. The red, finely granular kidneys weighed 340 gm. There was extreme hyalinization of the vasa afferentia and moderate hyperplastic thickening of the interlobulares. A good many hyaline glomeruli were seen; others showed periglomerular fibrosis. In a few glomeruli, areas of necrosis were seen. In many of the tufts, proliferation of the endothelial cells had occurred so that they appeared rich in nuclei; in these glomeruli, the capillary loops were almost entirely devoid of red cells, being filled, in many instances, with a pink staining amorphous substance. The tubules showed well marked degenerative changes. Interstitial fibrosis was prominent, and there was considerable round cell infiltration.

CASE 6.—E. F., a woman, aged 34, when operated on for hernia, a year and a half before admission, was told that she had high blood pressure. The chief complaints on admission were dyspnea on exertion and precordial pain and dizziness, both of about a year's duration. There was no history of nephritis, but during her last pregnancy, a year before, she had had some disturbances evidently correlated with the hypertension. On admission, she was somewhat dyspneic and cyanotic. The blood pressure was 208 systolic, 132 diastolic. Albuminuric retinitis was present. When admitted, the renal function was not severely impaired; the phenolsulphonephthalein output (intramuscular injection) was 35 per cent. in two hours, and the blood chemistry findings were: urea nitrogen, 19.6, and uric acid, 1.8 mg. per hundred cubic centimeters. For about a month, her condition seemed somewhat improved, but then she became stuporous and evidence of renal insufficiency appeared, the blood urea nitrogen mounting to 67 mg. per hundred cubic centimeters. During this period, a left hemiplegia appeared. She was comatose during the last week of life.

Necropsy was performed. There was a fresh hemorrhage in the region of the right internal capsule. The heart weighed 700 gm.; there was very marked hypertrophy and dilatation of the left ventricle. The finely granular kidneys weighed 300 gm. The smaller arterioles showed well marked hyaline-fatty intimal thickening. There was only slight elastic hyperplasia. Only a few glomeruli had been hyalinized. Most of the malpighian corpuscles contained few or no red cells in their loops. In some, considerable proliferation of the nuclei of the tuft was present. The glomerular capsules showed no evidence of epithelial proliferation, but some of them contained pink staining exudate in the capsular space. The tubules showed only slight regressive changes. The arterioles of the pancreas, spleen, and, to a lesser extent, of the liver, showed moderate hyaline-fatty intimal thickening. The changes in the renal parenchyma were not very marked and might be interpreted as a rather slight acute nephritis were it not for the well marked arteriolar changes, the few hyaline glomeruli, the enormous cardiac hypertrophy and the history of hypertension, known to have existed for a considerable time.

CASE 7.—R. W., a woman, aged 71, admitted, Sept. 26, 1923, had had diabetes for years. She had had transitory hemiplegia, a few years before. She had felt well till five weeks before admission, when swelling of the feet, incontinence of urine and mental deterioration set in. She was stuporous when admitted. The blood pressure was 190 systolic, 92 diastolic. Albuminuric retinitis was present. The urine contained sugar, albumin and numerous hyaline and granular casts, but no acetone bodies. Despite the presence of considerable sugar, the specific gravity was only 1.020. The blood sugar, on admission, was 465 mg. per hundred cubic centimeters, reduced to 165 mg. by insulin. The blood chemistry findings were: October 1, urea nitrogen, 51.9, uric acid, 5.3, creatinin, 3.1, and sugar, 151; October 3, urea nitrogen, 82.7, and sugar 240 mg. per hundred cubic centimeters. The patient died, October 6, after prolonged coma (not diabetic).

Necropsy was performed. The heart weighed 620 gm.; all chambers were hypertrophied and dilated, the left ventricle most markedly. The pale, finely granular kidneys together weighed 180 gm. There was marked arteriolosclerosis. There were numerous hyaline glomeruli and atrophic tubules. The majority of the glomeruli were not, however, hyalinized. They exhibited well marked proliferation of the nuclei within the tuft, the capillaries of which were often collapsed or filled with an amorphous, pink staining substance, and were mostly devoid of red cells. Bowman's capsule, in these glomeruli, seemed normal.

These cases illustrate that renal insufficiency may complicate essential hypertension despite the fact that much of the parenchyma has escaped arteriolosclerotic atrophy and obliteration. The glomeruli that have not undergone hyalinization then exhibit proliferative changes which are not present other than minimally in cases with intact renal function. The original opinion of Volhard and Fahr that these changes, which they interpreted as inflammatory, are due to toxic substances of endogenous or exogenous origin injuring a kidney rendered susceptible by already existing arteriolosclerosis, is not supported by adequate evidence and has not met with assent. Neither clinically nor anatomically is there proof that any other pathogenetic factor than the small vessel sclerosis plays a part in the production of the renal lesions in these cases with uremia. It seems very probable that the proliferative changes in the glomeruli are to be regarded as merely a reaction to a rapid course of the arteriolar process, i. e., as analogous to the reaction at the borders of an infarct. I [29] have observed similar proliferation of the nuclei of the glomerular tuft as well as leukocytic accumulation in the capillary loops in a case of periarteritis nodosa in which the vasa afferentia were very acutely involved. Weighty evidence that the arteriosclerotic process in these cases has a more rapid tempo than in the cases without uremia is afforded by Fahr's [27] statistics, which show that in cases of essential hypertension with associated uremia the patients usually die at a younger age than in those cases not terminated by renal insufficiency. This is borne out by Cases 5 and 6. Were renal insufficiency in essential hypertension usually due to the progression

29. Fishberg, A. M.: Zur Kenntnis der Periarteriitis Nodosa, Virchows Arch. f. path. Anat. **240**:483, 1923.

of the slow obliteration of renal parenchyma till the factor of safety is exceeded, death from uremia should occur at a higher average age than death from cerebral hemorrhage or cardiac failure. But this is not the case.

Clinically and anatomically, the cases of this group may be divided into two stages:

1. A phase of pure hypertension. Though the patients may have no symptoms during this period, which often stretches over many years, its existence is proved at necropsy by the arteriolar changes and the great cardiac hypertrophy, which are obviously not of recent origin.

2. A phase of renal insufficiency, usually of comparatively brief duration. This is apparently coincident with the onset of the glomerular reaction, the histologic characteristics of which indicate its brief duration. The central point of the whole problem—what causes the change from the first, relatively benign, stage to the second period with its fatal renal insufficiency—is totally unexplained. We do not know, aside from the rare cases included under Group 1, why this transition to the stage of kidney insufficiency occurs in so small a proportion of cases of essential hypertension, while the large majority never develop renal symptoms. Whether this change is due to the addition of a functional vasoconstriction to the already present arteriolosclerosis,[26] or is to be attributed to an acceleration of the arteriolar lesions per se, cannot be said. In contradistinction to nephritis, the reactive changes in the glomeruli are not extensive enough to be regarded as the cause of the uremia. They are merely reactions to, and indicative of, the rapid arteriolar process which, by interfering with the circulation through the kidney, is the actual cause of the renal insufficiency.

3. *Evidence of Cardiac Insufficiency.*—In four cases of the foregoing series, moderate increase in the nonprotein nitrogen of the blood (to over 40 mg. urea nitrogen per 100 cubic centimeters) was present. In each of these cases, there was severe cardiac insufficiency, evidenced at postmortem examination by chronic passive congestion of the various organs, including the kidney. In view of the predominant involvement of the renal arterioles by the arteriosclerotic process, it is seen that in essential hypertension the kidney forms a locus minoris resistentiae in the circulation. It therefore suffers from myocardial insufficiency before the other organs, with resultant albuminuria and increase of the nonprotein nitrogen of the blood. In confirmation of this view, I have repeatedly observed that increase in nonprotein nitrogen occurs much more readily in cardiac failure secondary to hypertension than when the circulatory insufficiency follows valvular lesions. The accumulation of nitrogen in the blood thus engendered is usually slight or moderate, not being much above 40 mg. of urea nitrogen per hundred cubic centi-

meters in any of the foregoing series. I have not seen symptoms of urinary intoxication attributable to cardiac failure alone in the absence of very severe lesions of the kidney or urinary obstruction. Increase of blood nitrogen due to cardiac insufficiency is usually readily differentiated from beginning renal insufficiency by the high specific gravity of the urine, which is "cardiac" in all its characteristics.

RECAPITULATION

1. In seventy-two cases of essential hypertension coming to necropsy, lesions of the terminal arterioles (arteriolosclerosis) were invariably present.

2. In every instance, the minute arterioles of the kidney (vasa afferentia and interlobulares) were affected.

3. The splenic arterioles were affected in about two thirds of the cases, the pancreatic in about half, the hepatic in less than a third, and the cerebral in about one fifth. The lesions in these organs, when present, were not nearly so marked as in the kidney.

4. The terminal arterioles of the skin, skeletal muscles, myocardium, lungs, gastro-intestinal tract and thyroid were very rarely involved and then to only an insignificant extent.

5. The distribution of arteriolosclerosis is different from that of large vessel atherosclerosis; the latter has its site of predilection in the heart, brain and extremities, while arteriolosclerosis is most frequent in the kidney, spleen and pancreas.

6. The view that hypertension is due to the statically increased resistance offered by organic lesions of the arterioles is untenable. A true generalized arteriolosclerosis does not exist in association with essential hypertension and, therefore, cannot be the cause of the latter.

7. Changes in the arterioles of a nature similar to the arteriosclerosis of essential hypertension occur physiologically with advancing years. Arteriolosclerosis is a pathologic exaggeration of these physiologic changes, resulting from the increased wear and tear incidental to the hypertension.

8. The anatomic changes in the kidney cannot be reconciled with the theory that essential hypertension is due to a disorder of renal function.

9. Only five of seventy-two cases of essential hypertension coming to necropsy had renal insufficiency. Increase in the nonprotein nitrogen of the blood in essential hypertension may occur in three ways, anatomically characterized by:

a. Coalescence of the arteriolosclerotic foci in the kidney.

b. Occurrence of more or less diffuse reaction glomerular changes.

c. Evidence of cardiac insufficiency.

Book Reviews

LECTURES ON PATHOLOGY. By LUDWIG ASCHOFF, M.D., Professor of Pathologic Anatomy, University of Freiburg. Delivered in the United States, 1924. Thirty-Five Illustrations.

This book contains a number of lectures that were delivered by Professor Aschoff, during his recent visit to the United States. It includes, among others, the Lane Lectures of Leland Stanford University, the Janeway Lectures of the Mount Sinai Hospital, New York, and the Osler Memorial and the Harvey Lectures.

Altogether there are fourteen separate papers. The subjects discussed are varied. They cover a wide range of pathologic data and evidently are not intended to form a consistent series. All, however, are concerned with subjects vital to medicine at the present time. Among these subjects, one finds the following: the reticulo-endothelial system; the pathogenesis of human pulmonary consumption; concept of inflammation; pathologic fatty changes; the normal and pathologic morphology of the suprarenals; atherosclerosis; ovulation and menstruation; the orthology and pathology of the extrahepatic passages; the site of formation of bile pigment; thrombosis; the relation of mucosal erosions to the development of ulcers of the stomach; the goiter problem, especially the goiter of puberty; renal secretions, and renal diseases.

It is impossible, in this review, to give a resumé or even to state the main conclusions of the author. On all these problems, he has worked and written for years, and these lectures are really condensations of his numerous papers and monographs. For that reason, many physicians will find this book most useful in obtaining fairly concise statements of Aschoff's voluminous writings

Of greatest interest, probably, are his discussions of the reticulo-endothelial system and the pathogenesis of human pulmonary consumption. More especially, Aschoff discusses, in connection with the reticulo-endothelial system, the morphology and origin of its elements, and then takes up the reaction of these cells in various pathologic processes, laying stress particularly on their relation to blood destruction, to bile pigment production, to their participation in general metabolic functions, such as the metabolism of fat, the metabolism of proteins, and their relation to the storage and metabolism of iron. Of particular interest, too, is his discussion of this system in relation to defense reactions and ferment production.

Aschoff presents concisely his well known views on pulmonary tuberculosis, emphasizing the importance of recognizing a primary infectious stage, characterized by an exudative, rapidly caseating bronchopneumonia, which is usually single. There may be a reinfection, which is usually multiple; this often occurs at the apex of the lung and results commonly in a process of cicatrization and contraction, this forming the productive type of phthisis.

His concept of inflammation is founded on a broad biologic basis. He analyzes in detail the various factors entering into this process, and presents an interesting but exceedingly complex tabular representation of the inflammatory reactions.

Aschoff emphasizes the complexity of the process of thrombosis and discusses several factors in the formation of thrombi. He takes up so-called spontaneous thrombosis, presenting in a masterly way its morphology and the mechanics of its formation. This chapter is recommended especially to the surgeon for his careful consideration.

Attention is called to the interesting chapter on mucosal erosions. Here appear many statements bearing on the origin and prevention of ulcers of the stomach.

To those interested in the study of goiter, his morphologic discussion of the problem will be of interest. He also draws many comparisons between the disease as it appears in Europe and in this country.

The author has a wide range of detailed information not only in the field of morphology, where he stands supreme, but also in biochemistry, bacteriology, immunity, and especially in comparative pathology. From all these sources, he utilizes and correlates important data in the elucidation of disease processes.

THE PHYSIOLOGY OF EXERCISE. A TEXTBOOK FOR STUDENTS OF PHYSICAL EDUCATION. By JAMES HUFF MCCURDY, A.M., M.D., M.P.E., Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Mass.; Editor of the American Physical Education Review. Illustrated. Pp. 242. Philadelphia: Lea and Febiger. 1924.

This book was written to serve as a guide and text for students and teachers of physical education, and most of the material presented was obtained through studies carried on over a period of more than twenty years at the International Young Men's Christian Association College at Springfield. There is an extensive bibliography, and frequent references to the literature on the subject are made. It deals largely with the effects of exercise and the various forms of athletic contests on individuals, both in regard to general constitutional effects and to the influence of exercise on the various organs, with particular emphasis on functional changes.